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HUMAN GENOME INITIATIVE

HEARING

BEFORE THE

SUBCOMMITTEE ON SCIENCE, TECHNOLOGY, AND
SPACE

OF THE

COMMITTEE ON COMMERCE,
SCIENCE, AND TRANSPORTATION
UNITED STATES SENATE

ONE HUNDRED FIRST CONGRESS

FIRST SESSION

ON

THE HUMAN GENOME INITIATIVE AND THE FUTURE OF
BIOTECHNOLOGY

NOVEMBER 9, 1989

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HUMAN GENOME INITIATIVE AND THE FUTURE OF BIOTECHNOLOGY

THURSDAY, NOVEMBER 9, 1989

U.S. SENATE,
Committee on Commerce, Science, and Transportation,
SUBCOMMITTEE ON SCIENCE, TECHNOLOGY, AND SPACE,
Washington, DC.

The subcommittee met, pursuant to notice, at 10:05 a.m., in room SR-253, Russell Senate Office Building, Hon. Albert Gore, Jr. (chairman of the subcommittee) presiding.

Staff members assigned to this hearing: Mike Nelson, professional staff member, and Fiona Branton, minority staff counsel.

OPENING STATEMENT BY SENATOR GORE

Senator GORE. The hearing will come to order.

Let me express my gratitude to all of the witnesses who have agreed to join us today. I am really looking forward to this hearing and the discussion it will entail. Our guests are also most welcome. We are delighted to see everyone this morning.

We are going to look at the human genome initiative today, a major new scientific undertaking for which this Subcommittee shares oversight responsibility. It is truly an extraordinary project, one which scientists have looked forward to for a long time but one about which most Americans know very little, and need to know a great deal more.

I had the opportunity eight and a half years ago to chair the first hearings on this subject on the House of Representatives side, before there was a human genome project, and we looked at a lot of the same questions that continue to arise. Of course many new questions have also been stimulated as work has gotten underway in earnest.

Two years ago, debate about the human genome initiative raged within the scientific community. There were arguments about whether it should be done at all, arguments about which government agencies should take the lead and arguments about the focus of the project and how fast to go.

For those who followed that debate, it was really quite exciting. We were witnessing something very special, the birth of a true revolution in science in an age when there are so many revolutions in science.

Today we will learn that those debates have paid off, and we are fortunate in this country to have put in place a program which

seems to be well coordinated and which will help scientists do what they do best.

But there are still some problems, and while we are off to a promising start there is, of course, plenty left to do. As is increasingly the case in programs of this size, we will not only need to work together as a Nation, but we will need to work together on an international scale, as well.

How can we do that with fairness to all participants? After all, there is nothing the world's many citizens have more in common than our genetic heritage.

We will need to be ready for the vast influx of data from around this country and from around the world. There will be challenges to our skills in information management and technology transfer, both areas of keen interest to this Subcommittee.

Indeed, we have had a number of hearings and investigations into data handling ability and information management challenges, and one of the things we will hear today is that the information super highway network that this Subcommittee has pushed hard would be of tremendous benefit to the human genome initiative.

The public must be included as active participants in the dialogue about the human genome initiative. One of the goals of this morning's hearing is to encourage broader public discussion, to make sure this subject, which at times seems too complicated and too easy to avoid, makes its way onto the American agenda.

In that regard, I want to applaud those in charge of this program at NIH, at least, for setting aside a minimum of 3 percent of the overall budget for public education and the study of ethical, legal and social questions. We will talk with DOE folks about what they are doing in this regard, also.

Many have said that the tools emerging from this project to map the human genome will be the most important and powerful that science has ever provided, resulting in changes even greater than those brought about by atomic power or the computer revolution.

I do not think those are overstatements. What makes us unique among all living things on earth is our ability to develop mental blueprints of the world around us and then manipulate those blueprints and in the process gain power to manipulate the world itself. Discovery of a blueprint for human life will of course, then, inevitably confer new powers that must be used with great wisdom.

Listening to how the human genome map could help us prevent and treat the 4,000 known inherited diseases caused by single gene defects is itself really breathtaking, not only for the hope it offers but for the serious questions it raises.

I mentioned the hearings eight years ago on the application of biotechnology to human beings. The first hearing of that series looked at the use of genetic testing in the work place. In that hearing and many subsequent hearings, important questions about ethics, law and the impact on society were raised, including many that still have not been satisfactorily answered.

Fortunately, up until now these questions have remained largely theoretical, but this project will take us several steps closer to the point where these issues must be faced.

The human genome initiative is in my view a good example of the contrast between how well we are able to organize the scientific exploration of questions of science and how difficult we find it to delve into ethical and societal concerns that are also raised. Here, as has so often been the case, our cleverness has outpaced our wisdom.

Just to take one example to illustrate the point, recently the Senate passed the Americans With Disabilities Act, historic legislation protecting the rights of the disabled. Will that legislation protect those who test positive for a genetic disorder but have shown no symptoms of illness or disability? That is only one of many, many important questions we need to answer.

Our ability to reconcile the promises and the risks of biotechnology has come a long way in the 1980s. If we are to accomplish the dramatic progress we seek, we must be ready to roll up our sleeves and really dig into these issues. The Subcommittee looks forward to that opportunity today.

Let me recognize our ranking Republican member, Senator Pressler.

OPENING STATEMENT BY SENATOR PRESSLER

Senator PRESSLER. Thank you, Mr. Chairman, for calling this oversight hearing on the human genome initiative.

Identifying and analyzing, or mapping and sequencing, the human genome has the potential to do a great deal of good for society, but it also raises a number of difficult questions about the potential benefits and social implications of genetic engineering.

Biotechnology and genetic engineering are key technologies for the next century. The market value of American biotechnological products is already over \$1 billion per year and is expected to reach as much as \$40 billion per year early in the next century.

The biotechnology industry has the potential to help revive U.S. international competitiveness and to reduce our trade deficit. Last year, the United States exported \$900 million worth of biotechnology-related goods.

Through biotechnological research we can develop important new products for responding to the needs of the next century, such as drugs to fight AIDS and cancer, disease-resistant plants, animals that produce more food, and pesticides that are effective without being harmful to humans.

In South Dakota, for example, we are working to develop plants and animals that are resistant to extremes of temperature and weather at South Dakota State University's Bio-Stress Lab.

The human genome initiative will permit researchers to determine an individual's chance of developing a particular inherited disease. Perhaps eventually, through biotechnology and genetic engineering, we can wipe out all genetic disease.

But it also has the potential to cause a great deal of harm if the knowledge is not handled carefully. Who will have access to an individual's genetic information? For what purpose should it be used? How can we prevent discrimination based on genetic differences?

How much freedom of choice will people have in making decisions based on genetic information? These are difficult but impor-

tant questions, and I look forward to the testimony of today's distinguished witnesses.

Senator GORE. Thank you.

I have an opening statement that the chairman, Senator Hollings, would like to have included in the record.

[The statement follows:]

OPENING STATEMENT OF SENATOR ERNEST F. HOLLINGS
HEARING ON THE HUMAN GENOME INITIATIVE
THURSDAY, NOVEMBER 9, 1989

The goal of the Human Genome Initiative is to determine what makes us human and what makes each of us a unique individual. By deciphering the genetic code, we will be able to diagnose genetic diseases, better understand cancer and other often fatal afflictions, and create hundreds of new genetically engineered products. The technology developed for sequencing the human genome will enable geneticists to sequence the genes of other organisms, enabling scientists to develop better crops and farm animals. In addition, this technology will provide new opportunities in genetic engineering and biomedical research. There are many other benefits of the Initiative which now can only be guessed at.

But is all this worth the \$3 billion price tag for the Human Genome Initiative? According to its supporters, the Initiative will revolutionize the life sciences. According to its detractors, it will divert precious resources from other critical biomedical research programs.

At today's hearing we will have a chance to examine the Human Genome Initiative and the benefits it will provide. We will examine just where we should rank it on our list of science priorities. This will not be easy in this case because sequencing technology is changing so quickly. For that reason it is not really possible to even know what the

final price tag will be. Somehow the Initiative must be designed so it can adapt as sequencing technology advances.

Many of the issues that we face in setting national science and technology policy crop up with the Human Genome Initiative as well. As with research in general, with the Human Genome Initiative we must strike a balance between Big Science and Little Science. As with the Space Station and the Superconducting Supercollider, we must learn how to work effectively with foreign partners on a project too large to be funded by just one country.

Technology transfer is another concern, both in the United States and internationally. How can we guarantee that American firms get the first crack at the technology that the Human Genome Initiative will provide, so as to stay ahead of our foreign competition in this critically important field? Currently, the United States has the lead in sequencing technology and biotechnology, but our European and Japanese competitors are coming on strong. We must make sure that the United States does not end up paying for the basic research while the competition collects all the profits.

I am glad that this hearing is being held; it will help the Senate determine its research funding priorities in these times of tight Federal budgets. We have some very distinguished witnesses here today, and I look forward to reviewing their testimony.

Senator GORE. We are real pleased to have as our first witness the Honorable Pete Domenici, our colleague from New Mexico.

Senator Domenici.

Senator DOMENICI. Would you like me here or there?

Senator GORE. Why don't you go right there? Either place you want. We want you here for your expertise as a witness, and you are also most welcome to join us after your testimony in questioning the other witnesses if your schedule permits.

But I want to acknowledge in introducing you that you have been an avid supporter of the human genome initiative since the first days of the program and have shown a particular interest in DOE's role in the human genome initiative.

You chaired some of the first Senate hearings on this initiative. You know the program very, very well, and I think it is safe to say that the current state of the initiative is due in significant measure to the knowledge that you displayed in early hearings and the impetus you gave the program.

You have been associated with DOE's role in it, but I am not sure NIH would have gotten up and displayed as much energy and creativity as it has if it had not been worried about DOE taking over the whole thing with you as its champion.

In any event, we are delighted to learn from you here this morning and we welcome your comments.

STATEMENT OF HON. PETE V. DOMENICI, U.S. SENATOR FROM NEW MEXICO

Senator DOMENICI. Thank you very much, Mr. Chairman, and Senator Pressler, it is good to be with you.

First, let me say to the Committee and to the NIH people who are here, whatever it was that got this program to its current status and whatever part I played, I am very pleased that we are now in a situation where the National Institutes of Health and the Department of Energy are working together.

The National Institutes of Health very recently put in charge of this program an eminent scientist. I happened to read the book of his early activities in England and in the United States which got him the Nobel—the great awards.

Then I asked somebody well, what has he been doing since then? About three months later I found out that he had a minor lull during which time he did a lot of great teaching at some great universities, and sure enough, about the time I was wondering, with genome going on full-speed ahead, where is he, NIH found him.

I then kind of wondered, when he was talking about internationalizing this activity, had a few comments to make about not necessarily agreeing with that, I wondered if the big lull in his activities had had some negative impact on his understanding of the deplorable situation that we have in the United States with reference to having the greatest science in the world and not being able to get the applications of that science into the American marketplace.

So I invited him up to talk to me and I must say that from that point on, which is a little less than a year ago, I am now a fan. I believe he is on the right track. I think he is committed to solve some major United States problems while he solves the genome

problem, but I also think he understands the scope of this genome research.

Let me add one comment. I compliment you and this Committee for this kind of oversight and effort to prioritize science efforts that the government is involved in and where we can to encourage better participation and coordination out there among our universities and private sector.

I would suggest one thing, Mr. Chairman, and I think you might find some rather receptive Senators. One thing wrong with our efforts to prioritize is that the Senate Committees, the Committee structure both here and in the House, has not come close to keeping pace with the changing times, and it is very, very frustrating, and it will be to you as you move through trying to put some of these initiatives into operation.

You are going to find that you are going to spend as much time with your staff and the parliamentarian trying to figure out how to get a bill through and the principal activity will be, is it our jurisdiction or somebody else's?

If it is yours, you know you can clear it and get down and have a real debate. If it is not, you will be before two or three Committees trying to solve some little tiny piece of a very significant science bill.

Senator GORE. Are you sure about this?

Senator DOMENICI. I am sure about this.

As a matter of fact, I want to thank you, because last year you wrote—believe it or not, one of the most significant technology transfer initiatives just got completed, and for those that wonder about our Committee system, it is going to be on the Department of Defense Authorization Bill, and you wrote a letter last year to Chairman Les Aspin at my request because we have a Technology Transfer and Competitiveness bill that tries to tap the huge resources of the Defense Laboratories, the Nuclear Deterrent Laboratories, the Department of Energy Laboratories.

Incidentally, Mr. Chairman, I want to make sure that the science community understands what Secretary Watkins now understands at DOE. The largest science organization in the world, in the free world, is the Department of Energy; 23,000 scientists, physicists, engineers and back-up people are in their laboratories.

That does not make them premier. It just means that we have to find a way to work together and we have to find a way not to isolate that resource community under any false pretense—national security.

You know, we have been clearing national security items in deterrent laboratories before we apply technology transfer activities, and we still have people in the United States Congress that do not understand that technology transfer aspects do not have anything to do with national security. They already—the security issue is already cleared.

But in any event, that new competitiveness bill for the national laboratories will have a great deal to do with the success of priorities that you end up setting here for science, because science will be working with those laboratories.

Science cannot work in individual institutions or disciplines any longer. That is a goner. When you can say forthrightly, as a leader,

that there will be more scientific break-throughs in the next 30 years than all of human history, you know and we know that that is dramatic.

That is not going to happen. That is not going to happen unless the disciplines work together, unless institutions work together, and I might add unless the private sector, the great research capability and development capability that they had finds its way into a more coordinated effort at making these break-throughs not only achievable, but applicable, in the American society.

Senator GORE. If I may add to your list and say that we must find a way to quickly link up the advanced computers within which enormous amounts of data are being organized and stored, so that the clusters of scientific expertise and the national labs and other parts of the scientific community can communicate using data flows of 3 to 10 billion bits per second so that we can send gene sequences, interactive graphics, computer models and the other ways in which data are now contained and transmitted.

Senator DOMENICI. The statement that we are going to make more breakthroughs in a short time frame, perhaps 30 years, than all of history is probably more related to the fact that we now have computers and supercomputers than any other single thing.

We still have the same brilliant scientists. It's just that it does not take them so long to get from A to B, and if we do it right, some things that would take a lifetime in a laboratory, medium sized laboratory, can be done in a month. And that is where this scoping has occurred.

But let us get to genome. Mr. Chairman, when you look at—when you look at what science ought to do, you cannot find a better science program than this one. For instance, if you look at why we would want to spend money on science, where we would find a better objective than wellness, than curing horrible diseases, many of which we think are hereditary.

Just look at the exhilaration that has come into the medical field and into the wellness field when we found one real genetic linkage, and we said we are going to solve the problem of cystic fibrosis? I mean, across the United States the cystic fibrosis organizations are having their fund-raisers, and they are talking about maybe we found the genetic linkage.

I was at one and a mother and father were there and three of their children, three out of four, have this, and they were in tears telling the crowd that maybe our scientists have found the linkage which will eventually yield the cure.

Now, what our people must understand is that those few breakthroughs—that one and a few others—that have been the result of scientists trying within this huge human genetic machine to isolate on it and find that one, if the genome mapping and ultimate sequencing works, we will be handing to the scientists, we will be handing an entire road map for them to take and apply just as they are going to apply the genetic information that has unlocked the mysteries of cystic fibrosis. Think of that.

You enumerated maybe 4,000 genetic ailments. We know there are plenty.

Senator GORE. Those are just the single gene defects.

Senator DOMENICI. That is correct. So, it seems to me that if you are looking for priorities, the first priority ought to be—and I say this in a very—in a very different framework, but the first priority for everyone ought to be to keep—get this American economy where its productivity and growth is occurring and continuing and reliable enough where these kind of exciting programs can be afforded by the American economy because make no bones about it, American science is the envy of the world. And the reason it is is because we spent a lot of money on it over the last 60 or 70 years because America had an economy that was robust, and so we have a lot of random science around.

We may not be able to afford that much random science. In fact, some of them may have to begin to really say where is the commercial value in the research. We may have to be that profane.

I am already telling them that. Some scientists do not like to hear it, but we might have to because commercial value of science is getting very, very important and while we want most of them to be random and doing their thing, we might have to ask some what is the commercial value and are you working with the private sector and are you working with the National Laboratories, the National Institutes of Health to an end that is discernable that would have some kind of marketplace value in the fields of health care, wellness, biomedicine or the like.

So, we are now up to about \$100 million a year between NIH and the Department of Energy. I think probably Los Alamos Laboratory will make the first chromosome mapping and move on to sequencing on chromosome 16. I do not know that it is the most relevant and significant at this point, but I think we will learn a lot from it.

The other part of the genome program that Dr. Watson has in, Mr. Chairman, is that the private sector, the largest of the companies for the most part, I hope it can get down to smaller companies also, but by farming out so as to speak some of the chromosomes with laboratory and institutional scientists and private sector expertise, we are moving ahead very well.

I hope next year the President asks for about \$200 million for the genome program split about like it is now. Perhaps we need another aspect, flexible money for the program. I am going to support that, and I urge his science advisor to do that.

On the other hand, we all know that there are many areas of future potential for science in the marketplace of America and the world and in the problems of America and problem solving of the world, and perhaps there are some that are more important than this one. I do not know of very many.

This is a long-term one, but it may be one of the most important ones that we attempt to work on as a nation.

So, Mr. Chairman, I think you are to be commended, you and the committee, for the work you are doing in an effort to make more sense out of the programs of science.

It is very, very difficult to evaluate them the way we do business around here.

I would tell you that I look for a budget next year from the executive thanks to the National Academy of Science, and I went to bat for them once they got it to us.

We will have, I think, a separate addendum to the budget on science programs within the government so that we will be able to budgetarily take them out of their line role into a science budget. That's just a little first step but it is indeed helpful because it permits committees like this one and others to get out of the evaluation of the bureaucracy that it is in and evaluate it in an overall scheme of things, and I think that is good.

That is about all I have to say. Let me just admonish the committee. I do not think we ought to let this research languish because it has problems of ethics and other issues. I think we ought to solve those, but clearly the pluses for humankind on this kind of program are probably—in the field of wellness and health are probably the most significant in all of medical history, and we have to find ways to solve the other problems.

We cannot let anything get in the way of solving human illness, genetic defect problems, at least in this Senator's opinion, and I think there is a way to solve the concerns about genetic manipulation and the like.

Thank you all very much.

Senator GORE. Thank you very much. Pete, I know you have got the Budget Committee and the Energy Committee and other matters on your schedule. But if you do have time, you are most welcome to come and join us. I do not have any questions. I just wanted to thank you for getting us off to a good start.

My colleagues may have questions.

Senator PRESSLER. I have just one quick question.

Pete, you mentioned the committee structure here and how Congress reacts to science and how science is getting ahead of us in terms of Congress as an institution. It is awfully hard for us to focus on some of these scientific developments because we have so many committees that divide up the responsibilities. We have to go through the budget process, including authorizing, and appropriating. What can we do organizationally around here to address a problem like this better?

Senator DOMENICI. Well, Senator Pressler, It is very difficult. It has just been a problem with this kind of institution for all of time, so far be it from me. Science would really leave us in the dust if we tried to wait around to reorganize this place. That normally takes—I have been on two of those, and we do not get much reorganization.

So, I think it is a matter of the people, the people here. So, if this chairman would like to have joint meetings, joint hearings on certain issues, I think if he asks, they will be done.

You would be amazed, however, that even if you try to do that, you still have the issue very, very much fractionated. For instance, the Judiciary Committee has a significant role to play in technology transfer and competitiveness as far as the National Laboratories is concerned.

And I guess if I were to give each of you a questionnaire and ask you why, unless you have been involved you probably would guess wrong. But it is the Freedom of Information Act which has an awful lot to do with whether a private sector will negotiate with the National Laboratory if they cannot retain a period of time

when their information is secret, which is always occurring in the private sector.

Well, we were hung up eight months, Senator, Mr. Chairman, on a bill once on that issue, and it had—we were about to get the entire competitiveness and technology transfer aspects of the National Laboratory changed. We lost the bill.

The next year we made headway and then three years later we got it through. But I think we just have to work around the system with people wanting to have joint activities. Energy Committee and this committee might consider next year some joint hearings in terms of prioritizing their activities, too.

Senator GORE. Well, I hope that will—I welcome that invitation, and we will certainly take you up on that. I know that Chairman Hollings will be interested to hear those comments as well, and I will certainly relay them to him.

On the committee reorganization I am afraid that the whole human genome initiative and the other 95 percent of the genetic data in the DNA will all be sequenced before the Senate committee structure is reorganized and rationalized, but I think you have given us a good road map there.

Senator DOMENICI. I think the other part, though, that I did not mention, Senator Pressler, and I should have and then I am on my way. Frankly, the appropriation process is very significant, too, because you cannot find any place within the appropriation process that you can find a priority system that—let us say this committee and two others in authorizing said here is our set of priorities. The funding is probably in four different appropriation bills, and that is not easy because you also have to bring them along from the standpoint of where do all the pieces of the puzzle fit, and that is a very tough one, Mr. Chairman. But it does need some thinking. There is no question about it.

Senator KERRY. I just want you to get us out of here by Thanksgiving.

Senator DOMENICI. I will try.

Senator KERRY. We are offering you a good deal. Just take it.

Senator GORE. Thank you very much, Pete.

[The statement follows:]

Pete V. DOMENICI
NEW MEXICO

United States Senate
WASHINGTON, DC 20510

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Statement by
Senator Pete V. Domenici
before the
Senate Committee on Commerce, Science, and Transportation
Subcommittee on Science, Technology, and Space

November 9, 1989

Mr. Chairman, I want to thank the Committee for holding this hearing to examine Federal research efforts on the human genome, and for allowing me to speak before you today.

You might call me a "true believer" in the human genome. Several years ago I introduced what I think was the first piece of legislation calling for a strong Federal commitment to mapping and sequencing the human genome. I am pleased that we are really starting to make that commitment, and I firmly believe we will benefit greatly from it.

Efforts currently underway to map and sequence the human genome could revolutionize our understanding of biology, and our ability to cure and treat literally thousands of diseases and ailments. The highly distinguished scientists who will testify before you today will surely give this Committee a much better description of the scientific potential of this project than I can.

I would like to tell you why I believe research on the human genome is very important to the future of our country, and should continue to be a Federal research priority. The human genome offers tremendous potential for improving not only biomedical science, but our nation's economic future as well. As we proceed with genome research I urge Congress, and I especially urge the scientists involved, to fully appreciate this latter aspect.

Research on the human genome is not simple biomedical research. Much of it right now involves developing tremendous new tools for that research. This effort requires the interaction of many scientific disciplines that must work together to develop new technologies that will speed the tasks of mapping and sequencing.

Perhaps even more importantly, we need to be concerned with how genome research -- as with all the research we do -- is eventually developed into useful commercial applications. We as a nation must see that the technologies and discoveries developed in the laboratories are fully transformed into

commercial products that will improve the quality of life for so many.

It was with these concerns in mind that I introduced the Department of Energy Cooperative Research Initiatives Act back in 1987. This legislation proposed establishing national research programs at DOE in three research areas that have tremendous scientific and commercial potential. The programs emphasized cooperative research between the DOE national laboratories, industry and universities. A human genome initiative was one of these three programs.

The heart of that legislation was a set of provisions designed to decentralize technology management within the DOE laboratories, encourage cooperative research with outside parties, and permit industry to have commercial protections for technologies developed in cooperation with these laboratories. This legislation was intended to establish a strong incentive for industry to brace new science initiatives developed at our national laboratories.

The human genome initiative I sponsored in that bill aimed to accomplish two things: to establish genome mapping as a federal research priority and to provide for a coordinated strategy of research and development by our federal laboratories and the private sector. Federal research is split principally between two agencies: the Department of Energy with its expertise in technology development and project-oriented interdisciplinary research; and the National Institutes of Health with its expertise in biomedical research.

The human genome initiative in that bill was later incorporated into a broader biotechnology bill I co-authored with Senators Chiles and Kennedy in 1988, known as the Biotechnology Competitiveness Act. That bill passed the Senate but was never completed in the House. I am pleased, however, that many of the ideas advocated in that legislation are being carried out anyway by the agencies involved.

Our fiscal commitment has grown dramatically over the past few years, with direct federal spending on genome mapping and sequencing up to nearly \$100 million this year. It is important to continue improving upon that commitment as it is needed.

I am also pleased to say that the heart of the original 1987 legislation I advanced will soon become law. Last week we reached agreement with the House of Representatives on legislation I and Senator Bingaman had included in the Department of Defense Authorization bill. Entitled the "National Competitiveness Technology Transfer Act of 1989," this legislation will establish many of the important

technology transfer changes we advocated in the 1987 bill, and will greatly enhance the possibilities for technology transfer from the DOE National Laboratories.

This legislation is also highly important for the human genome program since some of the most important genome research developments are occurring at several of our national laboratories -- one of which is in my home state of New Mexico: Los Alamos National Laboratory.

I am then generally pleased that we are making progress on both research and legislative efforts intended to maximize the benefits of genome research.

Yet, we still need to see that attention to the full potential of genome research is recognized, particularly at the scientist level. We must move beyond looking solely at the scientific aspects of our research, keeping in mind how the discoveries can eventually be used and what can be done to see that Americans benefit fully from our investment in the human genome.

Senator GORE. Let me call our first panel, Dr. James D. Watson, Dr. Robert Wood please come to the witness table.

Dr. Watson, among other things, of course, is Director of the Center for Human Genome Research at NIH. He is, as all here know, one of the world's foremost biochemists and eminently qualified to lead the human genome program.

As we all know, Dr. Watson and his colleague, Dr. Francis Crick, won the Nobel prize in 1962 for their discovery of the double helix structure of DNA, more than 35 years ago. Their work solved one of the central mysteries of human genetics and really made possible the work that we are talking about here today.

Our second witness on this panel, Dr. Robert W. Wood, is the Acting Associate Director of the Office of Health and Environmental Research at DOE, which oversees the DOE Human Genome Research program and funds genome mapping research at the National Labs, primarily at the Lawrence Berkeley Laboratory and the Los Alamos National Laboratory and at university research facilities throughout the country.

We are delighted to have the two of you here and genuinely appreciate the trouble you have gone to to make your appearance possible here today.

Dr. Watson, if you could begin, we are delighted to hear from you.

STATEMENT OF DR. JAMES D. WATSON, DIRECTOR, CENTER FOR HUMAN GENOME RESEARCH, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. WATSON. Mr. Chairman and members of the subcommittee, I am very pleased to be asked to speak today about the activities of the National Center for Human Genome Research at the NIH. I have a prepared testimony. It is, I think—fairly complete, and I will just summarize it in a few minutes.

Senator GORE. Very good. Without objection, the prepared statements of all witnesses today will be included in the record if they highlight them.

Dr. WATSON. Now, I want to start off by saying that if we were going to do the human genome project using today's technology, the way we do our science in laboratories throughout our country and the world, it would cost about \$30 billion. That would be under the assumption that it is going to cost maybe about \$10 a base pair, and we have to work out three billion of them.

Now, if you put that in terms of people, it is 300,000 person years. So, if you were going to do it, say, over 15 years, you would have 20,000 people, a good sized city just doing it. Now, that prospect is unappealing to everyone, and I think that is why when the idea for the project was raised people said no, we cannot afford it, and it would divert people away from something more important.

But we all feel now, and I think that was reflected in the National Academy report and the OTA report of two years ago, that there is no reason why we cannot get the costs down by a factor of ten. That will not demand any great conceptional breakthrough which would lead to the Nobel prize or anything like that. It just means organizing the research in a more sensible fashion and getting economies of scale, which means moving from groups of one to five people working together to groups of 20 to 50 people working together.

And if we organize in this manner, we think we can bring the costs down to a point where if we would do the project within a 15-year interval, it would cost, using today's dollar, roughly \$200 million per year.

Now, that is a little less than 3 percent of today's NIH budget, and I think that is a good bargain.

Now, I realize that money is very short today for many types of good science being carried out by our government agencies, and I am feeling slightly vulnerable that when someone does not get a grant and they think they should get it, they are told to blame me. So, I feel I have replaced Ronald Reagan as the cause of why people do not get their grants. It is an easy target.

Senator GORE. You do not have any trips to Japan coming up, do you?

Dr. WATSON. No, no, no, no. But the real cause of the dilemma which faces our community and our country as a whole is that we are just doing an awful lot of good science. The statement of Senator Domenici that the next 30 years will double the amount of good science is probably true because it is easier to do science. With computers you can do science faster, and it is particularly, I think, easy to do so in molecular biology.

I was at a promotions meeting at Harvard and Derek Bok asked why we never promote any of our chemists from being assistant professors, while all the biologists are coming up? I said, look, it is much easier within the timeframe of being an assistant professor to do something in molecular biology which is worth tenure at Harvard, whereas the chance of doing it as a chemist is harder.

So, we are in an era of just explosive possibilities. People are doing this good science, and when they do it, they want to be rewarded and if they do not get a grant, they have to feel mad.

So, we are faced with a situation where I think our true deficit soon will be—we should be spending about \$12 billion on health-related activities.

Now, I cannot tell you where it is going to come from. I am not going to make any suggestions, but that would just keep pace with the opportunities for doing marvelous things like you are going to hear about later today from Francis Collins. I mean, we have all these opportunities to use genetics to attack diseases which really just bring us despair.

Mental disease is something which one does not have to say how awful it is, how expensive it is, the tragedies to families involved. And we know there is a genetic component, and there are the techniques out there where in using genetics we might find the genes. If we find the genes, we may have the ultimate cause.

We see this most strikingly in cancer research. We really now have found oncogenes, genes which positively cause cancer. We are finding negative oncogenes, anti-oncogenes, genes which prevent cancer. We are going to understand cancer, and it is through the genetic approach.

And one does not want to say that from this knowledge we are going to cure major cancers, but I think, you know, someone will be against this if we do not pull it off because we really are getting the facts and we should push ahead as fast as possible.

And Alzheimer's is just grim beyond description. There is a genetic component. Francis Collins in his testimony has talked about it, and the genetic approach is one which we should use, and I think there is a sense of urgency.

So, the argument that we should put off the human genome program until we are sure we have got the costs down I think is—I would say it is immoral because the best way, you know, to combat alcoholism may be to find the genes which make some people particularly susceptible.

We had a meeting at the Cold Spring Harbor Laboratory recently on the genetics of alcoholism. It is a hard one because you have got to get family histories. Families do not want to tell you they are alcoholic any more than they want to say there is mental illness in the family.

But I think that if one goes at it in the way that Nancy Wexler did so successfully with Huntington's disease, getting the pedigrees, we can find the genes and if we get the genes, well, that is the most sensible thing to do.

So, I say we should go full blast with the program. Now, since our report has appeared two years ago when we said go ahead, I think it looks like an easier job. There have been technical advances in mapping and sequencing that make this reduction by a factor of ten look much more likely. So, I am not really worried about whether we can do it.

The other thing which particularly appeals to me is that there was the rumor, you know, that you had to be stupid to want to do such dull work. But, in fact, the people who are leading the program now—I will not speak for myself, but for my peers, they are fun to be with. They are really bright minds, and we are not dealing with people who cannot do anything else who are doing the genome. I think they are people who really see this as a great pro-

gram, and it is going to be a very exciting thing, not just 15 years from now, but just in working it out.

Senator GORE. We feel that way about you too, Dr. Watson.

Dr. WATSON. Now, Congress has asked us to prepare a national plan. We are working in conjunction with DOE and feel that it would be silly to have two plans, one from DOE and one from NIH. So, we have been working together. We will have a plan to present to you early in the year, and we have a joint advisory committee. I think the main reason why DOE and NIH can really work together very well is that we are friends and we respect each other.

And there is more than enough work for both of us and there are complementary approaches. So, I do not foresee any problems, and we are constantly talking to people and we are trying to set up joint committees. We do not want an informatics committee for NIH, one for DOE. It is silly. It is the same people, and we want just the best. So, I think there will be some division of labor, but whenever possible we are going to work together.

Now, as to our current objectives, and I will speak here of NIH—Dr. Wood can be more particular—one is we have to improve what we call the genetic maps; that is, locating genes on chromosomes, finding their exact spot. As Francis Collins can attest, that is absolutely necessary. You have got to map the gene before you can isolate it.

If you had not mapped the cystic fibrosis gene to a rather tiny place on a chromosome, then it would have been impossible. So, we see over the next five years the very crucial thing of getting good genetic maps for all 24 of the chromosomes.

Not only do you have genetic maps, but you have got to relate the genetic maps to the DNA itself, and we call these physical maps. And then we have got to get the DNA and overlapping sets of pieces and little bottles of given pieces of DNA, such as the cystic fibrosis gene, before you can sequence it.

So, you have got to start with the genetic maps, the physical maps, get the overlapping pieces of DNA, and these maps we can see ourselves getting within roughly five years.

The second part of the program is, of course, you have got to sequence the genome, and the biggest DNA molecule so far in sequence is that of a virus with a quarter of a million base pairs.

Now, an average human chromosome is about 100 million base pairs. So, the most successful project is a quarter of a million, and we think in terms of just getting a chromosome done. We have got to go up by a factor of about 400.

We are now at NIH soliciting grants, and we will probably give out four or five within the next year aimed at developing capabilities where labs can do one to two million base pairs per year at a cost which will come down to \$1 a base pair.

So, we will give people three-year grants, not five, monitor them closely. If they look like they are getting the costs down, then we will continue it because we have to essentially build up groups which can begin to work at about ten million base pairs a year. That means if they start five years from now, they can do a chromosome in ten years. So, we will finish it in that 15-year period.

Now, for megabase sequencing, we are going to have to use machines, and these machines are being developed. I think the best

ones—at least the commercial ones—are now being developed by the American instrument industry, and we hope that the American machines will be the ones that we will use exclusively. I cannot see any reason why the technology—right now it is the best in the United States—why we cannot keep it that way.

Now, when we get these sequences, we are going to have to handle the data, so it is a big informatics problem. It is a big computer problem, and it is essential that this be done well.

Currently, the DNA sequences are kept through an organization called Genbank in the United States.

There is a parallel storage group in the European molecular biology laboratory at Heidelberg, and they work together, share data, and people had said that it took too long between when the data were available and when they could be distributed back to the public. One is hearing now that this is actually being solved. So, I do not think there is going to be an informatics delay.

It does not mean that we will not have to have more people capable of analyzing the data. In these labs which are producing ten million base pairs a year, they are going to get about 40,000 to 50,000 base pairs of information per working day just coming out. So, you are going to have to have people capable of analyzing the information, and the key component in the NIH is going to be a training program which I think is going to emphasize particularly computer literate people who will know enough about genetics so that when we get the data, we can interpret it rapidly. And I will come back to this point of when you pass out the data.

Now, the last thing in our program I want to talk about is ethics. It is clearly very important, and I think the misuses of genetics which we saw in the United States before the Second World War and which were much, much worse in Germany during the war itself, the use of genetic reasoning for racial policies—everyone should know what happened and why people are worried it might happen again.

So, I think we cannot spend all of our money on ethics. We have to get the job done, but I see no reason why 3 percent should be a limit. I am very pleased that we have at NIH an ethics committee headed by Nancy Wexler. She can tell you in her testimony that follows mine where we are going, but we really want this committee to bring the general public in. It is not to be a committee representing us. It has really got to be very broadly based or there is going to be misapprehension.

That is not to say we think that the answers will be simple. In some cases, we will say we never answered them. But we have got to talk about them and know.

That does not mean you do not live because some questions do not have simple answers, but we want to have ethics be a strong component of the NIH Human Genome Program.

Now, another aspect of the NIH program is that in doing the human sequence we also have to do the sequence of some simpler organisms, starting with the bacteria. These genomes will be easier to do and easier to interpret. And so to build up to interpret all this data, we want to get practice, and it is not just practice on something that is dull. Knowing the complete blueprint for bacteria or for a fly is exciting.

And so the reason people are really doing it is they are scientifically excited, not just as practice, and we of course have to have a parallel program on the mouse because you can do experiments and if you want to know what a human gene is doing, what it is doing is probably very similar to what it is doing in the mouse at the biochemical level, and so we will work out an extensive program on the mouse.

Up to now you could say our grants have been largely exploratory. We have been giving out grants for two years. They have been chiefly to an individual in his own research lab.

As I said before, if we would go on just that way, it would cost \$30 billion. We have to build up more effective groups and so, we will have as a key part the creation of centers which may work out the sequence of a bacterial chromosome or might focus on the sequence of the fruit fly, *drosophila*, or might focus on a given chromosome. For example, we may have a center that will be the center of activity on chromosome 4, which carries Huntington's disease.

And it does not mean that all the work in the world will be done in that center. It will just be the coordinating place where you can get the job finally finished. But I think if we do not have the centers, we are not going to get the job done at a reasonable cost and in a reasonable time.

That is reflected in the DOE program where they are restricting their program largely to the National Labs where you can build up groups. We want to build up groups of similar size not only in our universities and medical schools but conceivably in some cases in industry itself. It may be that companies which are producing the DNA sequencing machines can go ahead and do it.

So, we are going to try everything. We are not sure what is the most effective. The only thing I am convinced of is if we give it to people who are not bright, we are going to waste our money. So, we have to see talent, but there is talent at a very large number of places around our country, so we are not going to restrict it to—it is not just going to be in the Bay region or something like that. It is going to be around the country.

Now, the last thing I want to speak about is international collaboration. The United States has the capability, the money and the brains to do the project all by itself. But I think the rest of the world really would be unhappy because it is not an American genome, and we could reduce the costs considerably if other countries would come in and play a major role.

I am in favor of it, and we have—are trying to set up a human genome organization which was given the name HUGO before the real HUGO arrived a short time ago. That HUGO really had power, whereas the genetic HUGO has no power now because it has no money.

So, to get it going we need money, and I think there are indications that we will get substantial money from the U.K., NIH and DOE, I think, will support it, but we want to be sure the other countries are coming in.

We do not want to just say we are going to set it up, start paying for it, and hope that other countries will finally share part of the

burden. I think if we set it up that way, they will never come and we will be stuck with the cost.

So, it is my hope that other countries will come in so we can do it. I think the thought that we will immediately share the data—and I know I am speaking for myself, not for NIH or for any members of the advisory committee, that sharing data without sharing costs strikes me as very unfair, and when someone does a small DNA sequence, they tend to interpret it. You do not do a DNA sequence, put it in a data base and tell people to go look at it.

And furthermore, some of this sequence is going to be commercially useful. I have no doubt about it. And so—you can ask Francis Collins about it, but the University of Michigan and the University of Toronto have taken out a patent on their work on cystic fibrosis, and if they had not, I think it would have been very stupid.

So, we have to realize there is an issue which has not been resolved as to how fast you will pass out the data. There are two reasons for that. I think, the best reason for someone doing the sequence is that they are going to be interested in the answer. If they are interested in the answer, they are going to want to have the fun of interpreting it themselves. Now, there is going to be so much data you can say that you cannot interpret it within a reasonable time framework, but I think we can do some searches, and that is a problem that has to be resolved within our own country and then within the world. But I do not think the answer is as simple as saying put everything in Genbank the moment you get it and let everyone have it. The people who are doing it will feel a little unhappy.

I remember being asked by someone, when you found the answer to DNA why did you not tell Linus Pauling? Well, we did not want to. I mean, we wanted to publish it ourself, and some people think that is immoral. You want to share the thing.

On the other hand, you know, if we had told Linus right away, I would not be here in front of you.

So, I think you have to really understand the motivations of why people do science and put the human genome in it and also see that our country's own interests are protected. That is my testimony. Thank you for allowing me to give it.

[The statement follows:]

Testimony by

Dr. James D. Watson, Director
National Center for Human Genome Research

National Institutes of Health

Public Health Service

Department of Health and Human Services

Thank you for the opportunity to present testimony on NIH efforts to map and sequence the human genome. I am pleased to testify as Director of the National Center for Human Genome Research on a program of immense importance to us all.

At the National Institutes of Health, the Human Genome Program is being managed by the National Center for Human Genome Research, established officially on October 1, 1989. The Center evolved from the Office for Human Genome Research, a coordinating unit within the Office of the Director, NIH, in recognition of the growth of the program over the last two years and the high priority NIH places on mapping and sequencing the human genome.

Overall advice and guidance to the Genome Program at the National Institutes of Health is provided by the Program Advisory Committee on the Human Genome. The Committee is working to promote coordination of NIH's Human Genome Program with the private sector, including industry, with various national and international scientific organizations, and with other federal agencies, including the Department of Energy, the National Science Foundation and the Department of Agriculture. The members of the Program Advisory Committee include representatives from academia, industry and non-profit organizations.

The task of determining the human DNA sequence is now firmly established as a national objective. Similar to the 1961 decision made by President Kennedy to send a man to the moon, the

United States has committed itself to a highly visible and important goal. We did not know if we could successfully reach the moon -- we already know it is possible to map and sequence the human genome. Though the final monies needed to completely determine the sequence of the three billion chemical components of human DNA called base pairs are ten times smaller than those needed to let Americans explore the moon, the impact of the Human Genome Program on human life is likely to be as great or greater.

Every gene is a unique fragment of DNA. These genes are strung along the 23 pairs of chromosomes present in every cell in the human body. Finding the location of individual genes on a chromosome and analyzing these genes down to their chemical components is now possible on a large scale. The National Institutes of Health has supported most of the basic research that has brought us to this threshold, especially the phenomenal explosion of biologic knowledge emanating from the invention of recombinant DNA technology in the early 1970's. Because of the generous funding provided by the Congress and the President to the National Institutes of Health, the United States is clearly the leader in this field of research.

The possibility of knowing our complete set of genetic instructions seemed an unreachable scientific objective in 1953 when Francis Crick and I discovered the helical structure of DNA. Then, there existed no way to determine the sequence (i.e., the precise structural composition) of even very short DNA molecules, much less the totality of human DNA. New techniques derived from

recombinant DNA technology have made it possible to isolate individual genes. Researchers can chop up DNA at identifiable points that act as landmarks, mix and match pieces of DNA in various organisms, grow unlimited quantities of these fragments in bacteria, and take DNA apart and put it back together again. They have learned to make DNA from laboratory chemicals and to note its tiniest variations. Scientists also have learned to "sequence" DNA, that is, determine the order in which instances of the four chemical components (abbreviated A, T, C and G) occur. Powerful sequencing techniques now make the sequencing of short stretches of DNA a routine laboratory procedure, although technology is still inadequate for the sequencing of long stretches of DNA at a reasonable cost.

Goals and Objectives of the Human Genome Project

The Human Genome Initiative is a worldwide research effort to advance the goal of analyzing the structure of human DNA and determining the location of all human genes. A more important set of instruction books will never be made available to human beings. In support of this larger goal, the project has several interrelated objectives:

- * Construction of a high-resolution genetic map of the human genome;
- * Production of a variety of physical maps of all human chromosomes and of the DNA of selected simple model

organisms, with emphasis on maps that make the DNA accessible to investigators for further analysis;

- * Determination of the complete sequence of human DNA and of the DNA of selected model organisms;
- * Development of capabilities for collecting, storing, distributing, and analyzing the data produced;
- * Creation of appropriate technologies necessary to achieve these objectives.

In 1988 the National Research Council convened the Committee on Mapping and Sequencing the Human Genome. The Committee estimated that a total cost of \$3 billion over a period of 15 years would be necessary to complete the Human Genome Project. This cost is far lower than the price we would pay for this information if we continued to accumulate it using the traditionally uncoordinated, but highly successful, support mechanisms that fund the vast majority of biomedical research. A major objective of the Human Genome Initiative is to acquire this information in a reasonable time and in a cost effective manner. I am committed to this goal. Considering the immense value of this information, a price of \$200 million a year, representing only a tiny fraction (less than 1%) of what this nation spends on biomedical research, is an excellent investment.

Benefits of the Human Genome Program

Gene mapping and analysis will be key tools of biology in the 21st century. When finally interpreted, the genetic messages

encoded within our DNA molecules will provide the ultimate answers to the chemical underpinnings of human existence. They will not only explain how we function as healthy human beings, but also provide us with a new understanding of such widespread illnesses as heart disease, hypertension, certain cancers and diabetes, that touch the individual lives of so many millions of our citizens. The sooner the entire genome is mapped and sequenced, the sooner scientists can get on with the real work of human biology: understanding what the genes do.

I believe that knowledge of our genes will be a key to further progress in medicine. Determining the location and structure of specific genes on the 23 pairs of human chromosomes is a major step toward discovering new methods to prevent or treat the 4,000 known inherited diseases that are caused by single-gene defects. The common chronic diseases, such as Alzheimer's, heart disease, schizophrenia, cancer and diabetes, also appear to have a genetic component. All these are multifactorial conditions where genetic predisposition as well as environmental factors play a role in determining who develops such diseases. These chronic diseases are responsible not only for much human suffering but also for the largest share of our health care costs. As human beings it behooves us to support this highly promising research initiative if only to provide us with a sound and comprehensive strategy for conquering these diseases. Without understanding the underlying genes involved, we are operating with our hands tied. It would be unthinkable

not to move forward in this important area of biomedical research when we know how to do it and when the potential benefits are so great.

Model Organisms

The sequencing of the genomes of relatively simple organisms such as bacteria and yeasts is intended to go hand-in-hand with, if not ahead of, that of the human genome. Experience has shown that information derived from studies of the biology of model organisms is a critical key in understanding and interpreting human biology. Knowledge of the simpler structures of the genes of bacteria and budding yeasts can facilitate the task of distinguishing the DNA sequences that actually carry a gene's instructions from the much more prevalent noncoding components whose functions are not fully understood.

Several research projects to determine the complete sequence of the DNAs of simple organisms are getting underway and NIH hopes to start funding a number of these in the current fiscal year. The size of the genomes being studied ranges from about 1 million base pairs to 100 million base pairs. The human genome, with 3 billion base pairs, remains a formidable objective. Considerable technology development will be needed before we can start sequencing the human genome at a reasonable cost. Sequencing of the smaller organisms will be used to improve sequencing technology, so that within 5-10 years, we will be able to start in earnest on human DNA.

Role of Research Centers

In order to accomplish some of these large objectives, we must design a strategy where economies of scale are sought and found. We need to establish research centers where groups of 15-20 individuals from many disciplines can pool their talents. These research centers must become the foci for collaboration with other investigators, for sharing and distribution of materials and equipment, and for data collection on an international scale.

The National Center for Human Genome Research has announced its plan to establish such research centers at academic and industrial sites, with three centers planned for fiscal year 1990. Additional centers are planned to be initiated in subsequent years. Research centers will be expected to address a coherent objective that is a major goal of the genome project. Some of these centers will focus on sequencing the genome of a model organism, some will focus on the physical map of a human chromosome, and others will focus on a particular technology.

Research centers can provide a stable environment for large, long-term projects and also will attract new investigators into the program. I want to point out that the Department of Energy has established three centers in their National Laboratories that are very similar in concept to the proposed NIH centers. I also expect that research centers will be established abroad and be funded by other nations.

Technology Development and Technology Transfer

Several significant improvements in technology have occurred in the last two years which advance our capabilities to map and sequence various genomes. There are now better methods that allow for the isolation and amplification of larger pieces of DNA. This facilitates the task of making physical maps because fewer pieces of DNA have to be assembled. Methods for localizing pieces of DNA on chromosomes using microscopes also have been improved. A third improvement is the application of a method called PCR, for polymerase chain reaction, to mapping. This is a chemical method for isolating and making large amounts of a desired piece of DNA. It allows specific segments of DNA to be located, even if they are buried in large amounts of other DNA. This method has had a revolutionary impact on the genome project and has made many experiments much simpler.

Recently, a proposal was made by several members of the original National Research Council Committee on Mapping and Sequencing the Human Genome that presents a system for collecting information from physical mapping projects in a common language. This new approach is referred to as sequence-tagged sites (STS) and will allow the data from diverse physical mapping techniques to be integrated into a common map. The STS proposal would also eliminate the need for large central repositories of DNA, as the information about STS locations could be used to regenerate any desired piece of DNA easily.

Although great strides have been made in technology development, there is still a need for further innovation to adapt the technology to large-scale projects and to bring the costs down. During the next five years there will be an emphasis on technology development in all areas of the human genome program. The ultimate technology that will be used to sequence the human genome may turn out to be a method that is still on the drawing board.

Rapid transfer of technology developed under the Human Genome Program to industries that can develop economically and medically useful applications is a major goal of the project. The biotechnology industry in the U.S. is strong and innovative and has close ties to the scientific research community. Industry has been a strong participant in all aspects of the Human Genome Program from the very beginning. Several members of our Advisory Committee and our various working groups represent the for-profit sector.

We also have awarded a number of research grants to private companies, both through the Small Business Innovative Research (SBIR) program and through regular programs. I fully expect some of our research centers to be funded in industry. We expect that industrial involvement will increase as the project proceeds, especially during the phase of large-scale sequencing. The commanding scientific lead enjoyed by the U.S. should not be allowed to erode, and we must help ensure that U.S. industry

reaps the benefits of the large investments made by this country in biomedical research.

Data Collection and Distribution

In the area of database development, the National Center for Human Genome Research will collaborate with NIH's recently established National Center for Biotechnology Information at the National Library of Medicine as well as with the Department of Energy. The National Center for Biotechnology Information was established to create automated systems for knowledge about molecular biology, biochemistry, and genetics; and to pursue research in biological information handling, particularly with respect to human molecular biology. Efforts of the National Center for Biotechnology Information are closely coordinated with the Human Genome Program through frequent staff interaction and through use of the same advisory groups.

Just last month Dr. Daniel Masys, Director of the Lister Hill National Center for Biomedical Communications of the National Library of Medicine, NIH, testified before your Subcommittee about current and future uses of computers and digital communications in the life sciences. Dr. Masys conveyed his strong support for high performance computing indicating its importance for accelerating biomedical discovery and improving health care for our nation. As one of the major products of the Human Genome Project will be large amounts of mapping and sequencing information, our Center also appreciates the need for

improving our nation's information infrastructure. A critical aspect of the Human Genome Project will be the design of appropriate databases to handle the storage, processing, distribution, and analysis of the large amount of data that will be generated. Such databases must be comprehensive, up-to-date, compatible with each other, and readily accessible to all scientists and clinicians who will need access to the data for their own research efforts.

Ethical and Legal Considerations

The plan to map and sequence the human genome is predicated on the belief that humanity will benefit immensely from related advances in medicine, biology, and biotechnology. Yet, many ethical, legal and social questions arise regarding the use of the information and capabilities that flow out of the Human Genome Program. Most of these ethical concerns are not new. We have faced questions regarding privacy, confidentiality and discrimination before with respect to diseases such as AIDS. Physicians and counselors frequently face such issues when treating patients with genetic diseases. However, with the quantity of new information that will emanate from the Human Genome Project, these questions will undoubtedly take on a new urgency and become relevant to a larger sector of the population.

The National Center for Human Genome Research regards these ethical, social and legal issues as a very high priority and is committed to providing support for studies that investigate such

concerns. Starting in fiscal year 1990, at least 3% of the NIH Human Genome Program budget will be available for activities that address ethical, legal and social issues related to the project. The goal of the ethics component of the Human Genome Program is to address, anticipate, and develop suggestions for dealing with such problems in order to forestall adverse effects.

The NIH Program Advisory Committee created an ethics working group, chaired by Dr. Nancy Wexler, to plan and coordinate this part of the Human Genome Program. Dr. Wexler is president of the Hereditary Disease Foundation and a neuropsychologist at Columbia University. The working group held its first formal meeting on September 14-15, 1989. At this meeting, the group began to develop a detailed plan for addressing the ethical issues arising from the application of knowledge gained as a result of the Human Genome Program. This plan will be available in early December and we will be glad to share it with you at that time.

In addition to focussing on the potential ethical, legal and social problems arising out of the Human Genome Program, we must also consider how unethical it would be not to pursue the project and to delay the possibility of prevention and treatment for those who suffer from genetic disorders. I believe that the benefits that come out of this tremendous research effort will far outweigh the real but avoidable risks. The key is using the knowledge gained from sequencing the genome in a responsible

manner and ensuring that there are plenty of safeguards to prevent any abuses.

NIH and DOE Cooperation

The National Institutes of Health and the Department of Energy have developed a remarkably close working relationship on the Human Genome Project. Mechanisms for the coordination of human genome activities between DOE and NIH are specified in a 1988 Memorandum of Understanding. A Joint Advisory Subcommittee was established to monitor and coordinate programs. Furthermore, there is extensive formal and informal interagency contact between program administrators.

This close working relationship was highlighted by a joint meeting of the advisors to the DOE and NIH which was held this past August at Cold Spring Harbor. The agenda was to prepare a joint NIH/DOE five year plan for the Genome Project. This was an exciting meeting because, for the first time, the question before us was not whether to start a human genome program, but how best to carry it out. The meeting was the culmination of the close cooperation between the agencies over the past two years and illustrated how the two agencies can bring complementary strengths to this project. It also was gratifying to see how much scientific progress has been made since the project commenced in 1987. A copy of the NIH/DOE plan will also be available in early December.

International Cooperation

The NIH is fully aware that the importance, complexity, and cost of the effort to map and sequence the human genome makes international cooperation desirable, if not essential. Most developed countries are already formulating strategies to undertake aspects of this international effort, and some developing countries are interested in participating in the research as well. To date, only the United States, the United Kingdom (U.K.), Italy and the Commission of the European Community (EC) have announced independent human genome initiatives, but there are good reasons for believing that France, the USSR, Japan, and possibly Canada will join the effort. International cooperation could significantly shorten the time required to finish the project.

How to ensure that nations work together instead of indulging in costly competitive races for the same chromosomal objectives will be a challenge. Open communication, sharing of basic scientific data and collaborative efforts are probably the most productive methods for preventing duplication of research efforts and costly international competitions. A number of prominent international molecular biologists and human geneticists have banded together to form "The Human Genome Organization" (HUGO). This organization is in the process of being formally established. We support the role of HUGO as the principal international coordinating group for human genome research. HUGO could greatly facilitate the free and open

exchanges of data that we all want to be features of the Human Genome Program. Knowing the sequences of half of the human chromosomes without having access to the other half would be unbearably frustrating. Sharing of the human DNA database is much more likely to occur if large-scale mapping and sequencing efforts are undertaken by all the major industrial nations that want to use the data.

Another challenge for us is to strike the proper balance between the necessity for international scientific collaboration and the need to promote the United States' competitive position in biotechnology. We do know that science cannot and will not advance when basic scientific data is shrouded in secrecy. By fully involving the U.S. industrial sector in the genome program from the very beginning we hope to ensure that these companies are in the best possible competitive position. The U.S. biotechnology industry is strong and leads the world in this field. There is every reason to think that they will meet the challenges facing them successfully.

Mr. Chairman, I am very excited by the prospects for the Human Genome Project. I am gratified by how much has already been accomplished both scientifically and in terms of international cooperation. The time to act is now and I am optimistic that we will be successful in carrying this project to completion. I would be pleased to answer any questions that you or Members of the Subcommittee may have about the Human Genome Program.

Senator GORE. Thank you, Doctor. A very enjoyable start to our hearing here today, and Dr. Wood, you have got a hard act to follow.

Dr. WOOD. I do indeed.

Senator GORE. But please proceed.

STATEMENT OF DR. ROBERT W. WOOD, ACTING ASSOCIATE DIRECTOR, OFFICE OF HEALTH AND ENVIRONMENTAL RESEARCH, DEPARTMENT OF ENERGY

Dr. WOOD. Thank you very much, Mr. Chairman. I am certainly pleased to be here to talk about the Department's Human Genome Program.

In your letter of October 25th to Admiral Watkins, you asked him to address the DOE role in the genome initiative, highlight some of our accomplishments, and talk about our future plans.

In my oral presentation I would like to summarize those three aspects of my written testimony.

With regard to the Department of Energy role in this activity, this is, in fact, a natural outgrowth of the historical DOE responsibility and the responsibility of its predecessor agencies, the Energy Research and Development Administration and the Atomic Energy Commission, for investigating the potential health effects of radiation and energy-related chemicals. This is a 40-year responsibility which started in 1946 with the creation of the Atomic Energy Commission.

For the past decade or more we have been increasing our efforts to use techniques of modern molecular biology to get at a more basic understanding of radiation and chemical health effects, and indeed the genome program is, as I say, a natural evolution of this effort to address modern molecular biology and to look at damage at the basic molecular level, the level of DNA itself.

As was mentioned earlier, if we can get an understanding of the differences between individuals' sensitivity, we perhaps can put on an individual basis an analysis of risk, and we feel that could have enormous benefits, both for assessing previous exposures of individuals and even being able to perhaps predict subsequent consequences. This would be a great help in terms of risk analysis and risk management.

Another aspect of our role is that we are responsible, as Senator Domenici said, for the national laboratory system, and we have within the national laboratories a unique capability in terms of the multi-disciplinary approach to problems that can be brought to bear on the biology, the physics, the engineering and instrumentation, and the computer sciences that, Mr. Chairman, you were talking about in your opening statement. We indeed do have that sort of a capability to focus this multi-disciplinary approach on significant problems within the Department of Energy system.

Within our programs, we are concerned with developing advanced technology for sequencing, new capabilities to carry out mapping, and an enhanced data and information management system. The challenge of organizing, entering, storing, retrieval, and analysis of the vast amounts of data that are going to come out

of this area—a very, very demanding and very, very challenging task, and, indeed, the key thrust of our program.

I might just underscore the words of Dr. Watson in reference of the cooperative joint effort between the Department and the NIH which, I believe, makes this not only a thoroughly enjoyable opportunity but, indeed, a very great challenge to work together in this area.

With regard to accomplishments in the DOE program, we might describe these under both evolutionary and revolutionary accomplishments. In the evolutionary sense, earlier techniques are now being improved. For example, an early sequencing technique which involves tagging the ends of a single strand of DNA with radioactive material, splitting it up, separating the pieces in gel electrophoresis, and then determining the sequence by measuring the radioactivity, is drawing upon a technique developed at the Oak Ridge National Laboratory about a decade ago called resonance ionization spectroscopy.

We can now enhance the sensitivity of that technique by orders of magnitude and thereby be able to use much, much smaller quantities of material to get this sort of information.

In a revolutionary sense, last winter, for the first time, a collaborative effort between the Lawrence Livermore Laboratory and the Lawrence Berkeley Laboratory obtained the first direct image of unstained DNA using scanning tunneling electronic microscopy.

This image showed the clear spiral helical structure that was predicted 35 years ago by Dr. Watson. This was a remarkable step forward and, since that time, this process has been repeated in a number of other laboratories.

The exciting future for that technique is that it may offer a completely new and different method of obtaining sequence information.

With regard to future directions in the program in the near-term sense, we will certainly continue to give emphasis to developing advanced sequencing and mapping technology, robotics, informatics, and particularly the network that I mentioned before that has to be set up, so that not only the national laboratories can communicate with each other together, but can tie in with universities on a national and even on an international scale.

The concern about ethics, and was mentioned earlier this is, of course, a very real and very great concern. We will be working very closely with NIH on this because, I believe, this is an issue that has to be addressed across the board, in the sense of exposures and the ethical concerns and considerations that must be addressed. So we will be working with NIH to wrestle with that very, very difficult problem.

Another point to emphasize that Senator Domenici has already pointed out is that the coupling with industry is important so that the technologies developed within the national labs can rapidly be transferred to the private sector.

Each of the national laboratories has been charged for several years now with implementation technology transfer to the private sector. In particular, we have charged the Los Alamos Laboratory with developing and being concerned with technology transfer in our genome program. They are interacting with industry to devel-

op techniques to facilitate this transfer, not only making sure that industrial communities participate in workshops, meetings, and symposia, but, where there is joint funding of programs within the national laboratory that gives private sector scientists an opportunity to work together with national laboratory scientists for periods of several months to develop these new capabilities.

Finally, in the longer term we see a real direction to and a real achievement in the biotechnology arena of a coupling between our genome research and another area that is exceedingly important and exciting now, our structural biology research.

The base sequence along the DNA molecule, in turn, determines the amino acid sequence in proteins and the amino acid sequence in the protein, in turn, determines the configuration or the structure of that protein, which is responsible for its functioning. So, this logical sequence from DNA to protein to the structure of the protein and to its functioning is really all put together, if you will, in this biotechnology arena.

We see the day when this may be integrated so that to engineering modifications at the DNA level, in turn, will be reflected in changes in the structure and in the function of the resultant proteins that are encoded in the DNA.

This, I believe, will be really the true potential for biotechnology. As has been discussed and will be discussed in the future, the implications of this in areas such as medicine and agriculture and, from the Department's point of view, bioremediation of waste and so forth are just enormously exciting and very, very real.

That will end my oral presentation. I thank you for your attention, and I will be pleased to answer any questions.

[The statement follows:]

Statement of Dr. Robert W. Wood

Acting Associate Director

Office of Health & Environmental Research

U. S. Department of Energy

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here today to discuss the status and achievements of the Department of Energy's (DOE) Human Genome Program. The aim of this focused program is to develop the resources and technologies that will lead to a complete description of the human genome at the molecular level. The Program represents a new approach, based on modern biology and technology, to the mission of evaluating the potential effects of low doses of radiation and energy-related chemicals on human populations. The knowledge gained will greatly enhance understanding of the molecular basis of genetic diseases, cancer, immune deficiencies, and individual susceptibilities and resistance to environmentally induced diseases. The Program is a direct outgrowth of four decades of DOE research, utilizing the unique capabilities of the national laboratories.

Interagency Coordination

DOE and the National Institutes of Health (NIH) are the only two Federal agencies with formal human genome programs. The DOE and NIH programs are coordinated under the umbrella of a Memorandum of Understanding (MOU). DOE, with a budget of \$27.6 million in fiscal year 1990 for the Human Genome Program, is emphasizing the construction of physical maps of each of the 24 different human chromosomes, development of the computational tools needed to enter, retrieve and analyze mapping and sequencing data in large databases, and development of new, innovative concepts and technologies for rapid, cost-effective analysis of DNA base sequences.

Postdoctoral training in all aspects of human genome research is also supported.

The NIH program complements that of the DOE by supporting: mapping and sequencing of model organisms; development of mapping and sequencing technologies; human genetic mapping; ethical issues related to clinical medicine; and predoctoral and postdoctoral training. The major part of the DOE effort is centered in national laboratories, while NIH supports work mainly in academia.

DOE and NIH, with the assistance of their respective advisory committees, are developing a national plan for the human genome program. We expect to submit the plan to appropriate Congressional committees in early 1990. Also, a study panel on ethical concerns of the Human Genome Program is being jointly planned.

In addition, coordination that also includes the National Science Foundation (NSF) and the United States Department of Agriculture (USDA) is conducted by the Genome Subcommittee of the Committee for Life Sciences of the Office of Science and Technology Policy Federal Coordinating Council for Science, Engineering and Technology (FCCSET). Although NSF and USDA do not have human genome programs, they are developing plant genome initiatives.

In the international arena there is a Human Genome Organization (HUGO) of eminent scientists. It was conceived in 1988 to assist with coordination

of national efforts; facilitate exchanges of research resources; encourage public debate; and provide information and advice on the implications of human genome research. Its current 220 members are from 17 countries and include 15 participants in DOE genome projects.

The Department of Energy Human Genome Program

As mentioned before, the aim of the DOE Human Genome Program is to provide resources and technologies that will allow the detailed, molecular level characterization of the human genome in a timely and cost-effective manner. A broad array of technologies and resources are being developed and will have continuing value. The techniques and technology created for mapping and sequencing the human genome will have enormous application in the biotechnology industry when applied to plants and animals of economic importance and to pathogenic organisms. Development of these techniques and resources requires a multidisciplinary and focused effort which includes biologists, engineers, chemists, and computer scientists. In recognition of this requirement and to facilitate transfer of newly developed technology to industry, former Secretary of Energy Helmington, in September 1987, established Human Genome Centers at Los Alamos National Laboratory (LANL) and Lawrence Berkeley Laboratory (LBL). The DOE program also includes a major program at the Lawrence Livermore National Laboratory (LLNL) and smaller efforts at other national laboratories and many universities. The overall DOE program is coordinated by several mechanisms, including frequent meetings of senior scientists, workshops, computer networking of key laboratories, and an annual meeting of all the scientists supported

by the DOE program. The first such annual meeting was held last week in Sante Fe.

Since its formulation in 1986 the DOE program has had three broad objectives. These are: (1) to develop advanced, cost-effective technologies for manipulation and characterization, including sequencing, of DNA; (2) to develop new technology for physical mapping and provide physical maps of human chromosomes in the form of ordered, overlapping cloned DNA fragments; and (3) to develop the computer capabilities needed to organize, disseminate and interpret the vast amount of data developed in the project. I will now discuss the status of our program in the context of these three objectives.

Walter Gilbert and Fred Sanger received the Nobel Prize in 1980 for their development of techniques to sequence DNA (that is, to determine the order in which DNA's four chemical components abbreviated A, T, C, and G occur in the DNA molecule). While these techniques have revolutionized our ability to analyze DNA and provide the basis for today's automated sequencing machines, considerable technological improvement is required before comprehensive sequencing of the human genome with its 3 billion subunits, will be cost-effective. A major component of the DOE program is the development of much faster and economical sequencing technologies. DOE is supporting two classes of approaches to improved sequencing, evolutionary and revolutionary.

The evolutionary approaches extend the methodologies of Gilbert and Sanger. One approach we have supported, called multiplex sequencing, developed by George Church of Harvard, is now licensed for commercial development. In another promising project at the Oak Ridge National Laboratory (ORNL), stable isotopes of a variety of elements are utilized to label DNA and a technique called resonance ionization spectroscopy, earlier developed at ORNL, is used for detection. This technology has the advantage of eliminating the use of radioisotopes, as were utilized in the methods of Gilbert and Sanger.

The revolutionary approaches are based on novel principles and instrumentation. Each has promise of great increases in speed but all are still in early developmental stages. I would like to cite two examples. Striking progress with the scanning tunneling microscope (STM) deserves mention. With this technology, specimens can be examined in a non-destructive manner and without specimen preparation steps which introduce inaccuracies. In 1988, a collaborative effort of LLNL and LBL utilized this technique to produce the first direct image of an unstained or uncoated DNA molecule. STM and other approaches for direct imaging of DNA are being explored for their potential for DNA sequencing. At LANL, efforts are underway to develop sequencing technology based on sequential degradation of the subunits from a DNA molecule. Each of the subunits is tagged with a distinctive fluorescent label and detected in a flow cytometer. Flow cytometry, a widely used technique for analysis and separation of cells and chromosomes and other biological particles, was developed at LANL some years ago.

The DOE program supports several projects aimed at developing physical maps of human chromosomes, a major goal of the program. Many DOE mapping projects, as well as other mapping efforts in this country and abroad, have benefited from a joint LANL-LLNL project begun in 1983 to prepare DNA fragments from each human chromosome. These chromosome-specific, cloned DNA fragments (libraries) are made available to researchers throughout the world through a repository at the American Type Culture Collection in Rockville, Maryland, supported by the National Institutes of Health. New approaches to physical mapping have been developed and are being productively applied in the DOE program. Mention should be made of the LLNL project to develop ordered clone maps of chromosome 19. This project developed new automated technology to establish clone order and is making substantial progress toward completion of the map. At LANL, a new mapping strategy was developed and is being demonstrated on chromosome 16. The strategy exploits the presence of repetitive sequences found in human DNA. Since these sequences occur on average about every 100,000 bases in the human genome, they provide a way to rapidly obtain ordered clones. These repetitive sequences previously had been regarded as a major impediment to mapping of the human genome. However, LANL in just a few months has completed over half of the physical map for chromosome 16. Other DOE-funded mapping efforts are currently focused on six other human chromosomes. Mapping technology is still under rapid development and the most efficient approaches are not yet clear. We are confident, however, that physical maps of all human chromosomes will be substantially complete in five years.

Developing the computer capabilities required for this project is the third goal of the DOE program. I will mention a few of the projects we are supporting to further these capabilities. It soon became evident in our mapping programs that the biologists would rapidly be overwhelmed by the logistics of tracking mapping results and recording the copious quantities of data generated. Consequently, LANL specialists, who have long been leaders in application of computer technology to biological problems, were called on to provide support in systems management, efficient data entry and data processing. An "electronic notebook" is being developed. It accepts diverse forms of raw data which can later be retrieved or processed by computational techniques. In the continuing development of these electronic notebooks, capacities to transmit data between collaborating laboratories and national data banks will be added.

A highly cooperative effort of DOE, NIH, NSF and the Howard Hughes Medical Institute, as well as international organizations is underway to define the most desirable characteristics of smaller temporary working databases and the larger more global human genome databases which will be required. It is particularly important that databases be developed which can accommodate data generated from around the world. This will require a high level of international cooperation. A long-term goal is to be able to easily track, from a single computer terminal, related information on physical maps, their associated genes, the structures and biochemical functions of encoded macromolecules, related data from nonhuman organisms and relevant medical information.

Other computer-related projects are oriented toward improving our capacity to rapidly analyze and compare DNA sequences so as to recognize relationships between genes and identify functional regions of their encoded proteins. One approach to improving this capacity is the further development of analytical software for general purpose computers. A complementary approach at the California Institute of Technology is underway to develop custom-made computer chips which allow a large number of analyses to be performed in parallel. This will allow analyses to be done much faster than on general purpose supercomputers programmed for the same analytical tasks. This capability is essential as data accumulates in the years to come.

The Future

Mr. Chairman, much has been spoken about many of the benefits which will flow from our acquisition of the sequence of the human genome. I am excited about the medical and scientific advances which surely will flow from this effort. The project is progressing very well and if history is any guide, will spin off important applications in each stage. Some implications of the genome project may, however, not be generally understood. When we obtain the sequence of the human genome we will have the linear code of all 50,000 to 100,000 human genes. The genome sequence will provide us with the basic molecular information about the genes which direct the functions of our body's many tissues. These genetic directions are in large part carried out through the actions of encoded proteins. Proteins act as three-dimensional dynamic structures. If we are to fully capitalize on the implications of modern biology and

biotechnology, we need to develop an understanding of the relationships between protein structure and protein function. Knowledge of these relationships is necessary to produce new and improved proteins that function better than nature's own. Protein engineering, because of its enormous commercial implications, will be a highly competitive field.

The unique resources within our national laboratories will have a major role in extending the benefits of the genome project to developing an understanding of macromolecular structure and function relationships. Several types of expensive and unique instruments at the national laboratories are in high demand for protein structural analyses because data is very rapidly acquired. These instruments include the High Flux Beam Reactor and the National Synchrotron Light Source at the Brookhaven National Laboratory, the Los Alamos Neutron Scattering Center, the Advanced Light Source under development at LBL and the projected Advanced Photon Source at Argonne National Laboratory. Although these instruments were developed initially by the nuclear and solid state physics communities, their utility for biological structure determination is now proven. Gathering X-ray crystallographic data for protein analysis formerly took days or weeks. Now only minutes are required to do this at the National Synchrotron Light Source. Future light sources will provide even greater capabilities. These facilities, all operated for the DOE as user facilities for the academic and industrial communities, are a unique and essential part of the effort to relate macromolecular structure and function. They will play a key role in the development of our national effort to develop biotechnology.

This completes my prepared testimony. I would be pleased to answer any questions that you or members of the Subcommittee may have.

Senator GORE. Well, thank you very much. We are going to abide by a time rule because we have four of us here today. Why do we not do a ten-minute rule if that is agreeable to my colleagues. Is that okay?

Are both of you satisfied with the degree of coordination between NIH and DOE at the present time?

Dr. WATSON. Yes.

Dr. WOOD. I certainly am.

Senator GORE. Now, I referred in my opening statement, Dr. Wood, to the decision by Dr. Watson to allocate at least 3 percent of NIH funding to the ethical and social questions that arise from human genome research. You do not have a comparable commitment at DOE, if I am not mistaken.

Dr. WOOD. That is true. We do not have set aside funds for that particular area.

Senator GORE. Should you not?

Dr. WOOD. We certainly will have an effort in that regard. We intend to work very, very closely with Dr. Watson and the committee that he has put together in this regard, so we intend to take it very, very seriously.

We have not to date set aside a specific percentage of the total funding for any given area. We will develop these areas and respond to needs as we see them developing over the next year or two.

Senator GORE. Well, with all due respect, I think that whether you set aside the money or not will be the signal of whether you are really taking it seriously or not. I would like to see not so much a duplicate of the NIH effort as I would like to see in the joint plan you develop a comparable commitment of money to that effort, wherever it is located, centered, organized, pursued because I think the history of science, particularly in this latest surge of the scientific revolution demonstrates very clearly that our cleverness outpaces our wisdom and unless we make the effort to anticipate and preemptively analyze the ethical dilemmas coming out of science, we will be overwhelmed by them.

This is particularly important where the human genome initiative is concerned because it is so easy to see the kinds of dilemmas you will be producing for us. To state it a little more strongly, I think that it is just intolerable to have a massive effort to compile this data base and have no commitment of money to the effort to understand the ethical, social, and legal problems that come out of it.

I applaud what the NIH is doing in this respect, and I hope that DOE will agree with what they have done and come forward with a similar commitment. Can you tell us if there is a strong likelihood that after this hearing you will go back and sit down with your colleagues and say you know, that subcommittee is right. We really ought to do that.

Dr. WOOD. We listen very carefully and closely to the advice. Yes, sir, we will certainly look very, very closely at that.

Senator GORE. Good, good. Thank you. I really hope you will. I am not kidding about that. I think that it is very, very significant.

Dr. WATSON. Senator Gore, we are talking with a very knowledgeable person trained in bioethics to head this section of our

office, and I would hope within the next month or so we can make an announcement of someone who will be joining our staff who has been trained in bioethics.

Senator GORE. Good, good.

Dr. WATSON. Who will handle the grant program and the general issues involved.

Senator GORE. Good. Well, I think it is so significant. I really do.

Let me turn quickly to the question of data management or informatics, as you described it, Dr. Watson. One of the other issues that our subcommittee has dealt with is the global environment. In that field, there was a discovery by a single British scientist of a huge hole in the stratospheric ozone layer above Antarctica.

After that discovery was announced, the U.S. scientific team went back and looked at the enormous amount of data that had been collected from our satellite observations and found that indeed, the data showed the ozone hole very clearly. It would have been discovered years earlier, but there was so much data that there were too few human brains to interpret it and alert the rest of us to what the data showed.

We have the LANDSAT program—and I often cite this example—where 95 percent of the pictures taken by LANDSAT have never been seen by human eyes, never fired a single neuron in a single human brain.

If we collect three billion base pairs and store them, how likely is it that the data will stay there in storage for a very, very long time before we interpret it? You understand the point I am getting at much better than I do.

Dr. WATSON. Yes. I think we will be interpreting some of it maybe 1,000 years from now because it is a very subtle message. I think what we want to do is to have a good first scan so anything that is pretty obvious—we would hate to do chromosome 21 and have the gene for Alzheimer's there staring you in the face and not find it.

To that extent, it is very important that we really train people to be capable of looking at DNA sequences, to really know enough biology to know what they are looking for because there is going to be so much data that unless you have a hypothesis to go at the data, you are just not going to—so we probably cannot train too many people to look at this data.

Senator GORE. Dr. Wood.

Dr. WOOD. Yes, I would like to comment on that, too. I think you are entirely correct. There is going to be a vast amount of data, and this calls for working early on—and we are giving emphasis to this now—to develop the formatting, organization, and standardization protocol if you will, that will determine how this information is entered and stored, and to develop the technology to make it available to a broad range of scientists, as I mentioned earlier, throughout this country and internationally so that an individual sitting in his laboratory at a university can have access to this data wherever it might be at a national laboratory, at an NIH center or whatever.

This sort of networking is something that we're going to give very great emphasis to and how to organize that.

Senator GORE. This subcommittee has been involved in advancing a plan for a data network, a network of information superhighways, if you will, and as I mentioned in my opening statement I believe that a computer network of that kind would benefit the human genome initiative. Would you agree?

Dr. WATSON. I would really have to defer because I am not an informatics person, and I do not have an intuitive feeling, but I think we would not be where we are today without computers, and I am sure the whole system has to be an order of magnitude better a decade from now if we are going to be—

Senator GORE. Will you be using computer graphics to analyze the data?

Dr. WATSON. Not in the sense of, Dr. Wood, of trying to go from the gene structure to an amino acid sequence to predicting the structure of proteins. There computer graphics is an essential operation, and one of the things you will want to do in using this information is to try and know what proteins you are going to make.

And we are—it is not yet a component of the NIH program to support this type of computer graphic work, but probably five years down the line as we begin to get real sequences, I am sure we will join in with DOE in supporting this type of work.

Senator GORE. Yes.

Dr. WOOD. Yes, if I might just add—we do employ computer graphics in the following sense at the Pacific Northwest Laboratory. They have developed a program in which you can take a whole chromosome and then layer by layer, if you will, get smaller and smaller graphical representations until you get all the way down to the sequence itself and locate where a particular segment might be on the chromosome.

Senator GORE. Right. Well, it is not difficult to imagine two groups of researchers on the trail of a single gene defect sharing a computer image of the particular chromosome and the particular gene sequence involved, turning it around, looking at it, comparing it to sequences on other chromosomes and having the ability to communicate in real time as they jointly work together and search for the answers they're seeking.

In order to have that kind of data flow back and forth, you have to have a very high transmission rate. But I will not belabor the point here.

Let me just complete my time here by asking you, Dr. Watson, about the cost of sequencing. It is \$10 per base pair now. You project it will be \$1 per base pair. Is that a limit? Could it go below \$1 a base pair?

Dr. WATSON. Actually, we really want to get to 50 cents a base pair.

Senator GORE. Well, we want to get lower than that if we can.

Dr. WATSON. Lower than that is going to demand an idea I haven't heard of yet.

Senator GORE. Occasionally such things as that come around.

Dr. WATSON. They do. We have—we welcome any grant applications from large business, small business, private, anyone who has an idea about reducing the cost of sequencing. We are funding a number of these.

But in front of you I am not going to promise something that I might not be able to deliver.

Senator GORE. Senator Pressler.

Senator PRESSLER. Thank you, Mr. Chairman. We complain a lot about our jobs here in the Senate, but one of the privileges we have is to be able to listen to a Nobel prize winner.

Let me ask you, I notice in your biographical sketch that you published these findings when you were 25 years old. Did you have a federal grant? How did you get it done?

Dr. WATSON. No. I had a grant from the National Research Council, which was actually money from—then called the Merck Chemical Company. I had a Merck fellowship, and then they fired me, and then I got a grant from the National Foundation for Infantile Paralysis, and that is how I was supported by postdoctoral fellowship at the time that we did the work.

Senator PRESSLER. That is very interesting.

Let me ask you about the Alzheimer's disease connection. Now, if it could be established that Alzheimer's is hereditary, would the human genome project help solve the disease? What has to be done to cure the disease?

Dr. WATSON. I want to leave this possibly to—give the question to Francis Collins because he is more closely connected to this type of work, but we will not know until we get the gene and we see how the gene is different in someone who is suffering from the disease. We may have a clue from just looking at this protein and what it does.

In the case of cystic fibrosis, it is what is called a channel, a molecule which lets small molecules move through the cell surface, and we just want—it might be a molecule which regulates gene expression. We do not know really what it is, but it probably will tell us how the disease starts.

So, I am just very curious, like everyone else. We want to get the gene, and we cannot tell you what we are going to do when we get it. But we know it is better than not having it.

Senator PRESSLER. Changing the subject slightly, in terms of social policy, and I certainly do not advocate it, but if one wanted to determine the parentage of welfare children or something of that sort in certain instances, how accurate is DNA to determine a father of a child?

Dr. WATSON. Totally accurate. That is sort of a perfect method. Originally there was some publicity when the analysis was slightly wrong, but it is getting better and better and there is no doubt now. If they say you are the father, you are the father.

What is worse is when they say you are not the father. So it is a wonderful tool in the proper hands, but I worry about fingerprints in the improper hands.

I think in this case there is a National Academy of Sciences committee now discussing fingerprints, and I hope that moves on, that report, to Congress, and I think some forms of legislation are going to be involved, just handling the privacy issue on fingerprints.

Senator PRESSLER. Yes. Now, there are some concerns that genetic engineering could lead to the ability to choose the genes of our unborn children and thus to create the perfect baby. How accurate is this perception? Is it a legitimate concern and should we be wor-

ried that genetic manipulation could destroy the genetic diversity of the human race?

Dr. WATSON. Now there is no way we can do any form of genetic intervention to human eggs. Whether that will be possible in some form in the future, I hope so. If you could do that in a way which worked, you might be able to take someone from a cancer prone family, add back another anti-oncogene, and then that family would no longer be a cancer family.

Now, that is a scenario in the good direction. Now, you may say there are so many scenarios in the bad that you do not even want to try the good, and that is the sort of question which I think our ethics panel and panels will be discussing for a long time. It is not a practical issue right now because we cannot do anything like that. And it may turn out we never are able to do it.

Senator PRESSLER. Thank you very much.

Senator GORE. Thank you, Senator Pressler.

Senator BRYAN. Thank you, Mr. Chairman.

Dr. Watson, you have been quoted in a recent article as being somewhat critical of the Japanese because they are spending far less than we are on this technology and if I understand the thrust of your comments, your concern—which I share—is that we will foot the bill and the Japanese, who have shown an amazing agility in transferring new technology into commercial application, will enjoy the benefits.

I guess my first question is do I understand the thrust of your concern——

Dr. WATSON. Yes, you do. And I think that——

Senator BRYAN. That makes two of us.

Dr. WATSON [continuing]. On the whole the Japanese have a very badly funded basic science program. When I visit them, I actually feel sorry for my good Japanese friends because their government really treats them miserably as they treat many of their other citizens.

But that does not mean we really have to subsidize them. I think it is the concern of the Japanese government to treat their scientists better, and so I am hoping that they will see the point because I think Japan viewing the United States as an enemy would not be rather good for Japan. But I think if they continue to proceed in this way, we have no choice but to regard them as such.

Senator BRYAN. And I would take it that the implication and logical extension of that is that we ought to withhold the products of our technological breakthroughs if they are not participants, at least on a pro rata basis of some kind?

Dr. WATSON. This is a difficult issue, and I think Maynard Olson in his prepared statement disagrees with me. He says we have to release the data.

I would take my time.

Senator BRYAN. Dr. Watson, my concern is in a little larger framework. You have suggested that international collaboration on these issues is important to us, and I think you discussed some interesting and promising work at the University of Heidelberg, if I understood your comment.

Dr. WATSON. Yes.

Senator BRYAN. I am concerned about how we can participate in this research and share this technology in a global sense. How do we as a country fulfill our international responsibilities to the world community, which I think we must do, and at the same time protect our national interest? In a very positive sense, in a very ethical sense, we want to realize the enormous prospects that this kind of research might make possible, but in a way so that commercial applications are developed, implemented, designed and manufactured by American manufacturers and not frankly, by our major international competitors.

Dr. WATSON. I mean, the first thing is we really have to keep our science better than any other country. I mean, we are now the best in biology.

Senator BRYAN. Agreed.

Dr. WATSON. Second is that we have to have the capital available to exploit this knowledge.

Senator BRYAN. Agreed.

Dr. WATSON. Many American biotechnology companies when they started obtained much of their original capital from Japan, and whether that was good or bad, I would have preferred that the capital could have come from the United States. So, we have to ask ourselves why capital had to come from outside the country.

Senator BRYAN. I would agree with both points that you make in your response.

When international cooperative research leads to significant breakthroughs that have potential commercial application, who gets the intellectual property rights? Who has the vested interest? Who has the proprietary ownership or is it kind of a free-for-all? If we fund all the research, then we have developed it, and hopefully American business will have the good sense, good judgment and financial capability to run with the ball. But if we share the costs, what happens at that point?

Dr. WATSON. Well, I think I will defer to Francis Collins because they have the cystic fibrosis gene, and it has been patented, and you can ask him why did he believe they could patent it, and how are they going to use it.

Senator BRYAN. Okay, that is fair.

Dr. Wood, I have a question for you about this vast bureaucracy that has evolved at the federal level. I understand the history with the AEC, ERDA, and now the Department of Energy. But wouldn't we be getting more bang for our buck so to speak, if we consolidated this effort under a single agency? What are the benefits to the American taxpayer of having this initiative bifurcated or trifurcated?

Dr. WOOD. I think the approach that NIH has taken over the years in managing its investigator-initiated research, if you will, is one approach to managing science in this country. We use that approach with our university program.

But also, as I mentioned earlier, the national laboratories do bring to bear this multi-disciplinary effort which can be mobilized and focused, and we have done that in the past. For example, I can think of the nuclear medicine field today, which derives in large part from the Atomic Energy Commission and for which we brought in accelerator physicists to produce isotopes, chemists to

work in radiopharmaceuticals, and engineers to develop the imaging instrumentation all of which comprise the field of nuclear medicine.

And I think that is the unique approach that the Department brings, and that is a role that we have played and we can and should play in this area.

Senator BRYAN. Dr. Wood, as you know, historically there has been criticism of your agency for not making available the technology it develops. Is DOE smoothing the pathway so that we can accelerate technology transfer and give us an opportunity to use the commercial applications. What is being done? What is being done to improve that?

Dr. Wood. That has been certainly true in years past. But, I would say over at least the past decade, there has been really quite a turnaround of the Department of Energy in terms of its interest in concern for and efforts to try to facilitate technology transfer.

There has been a broad change in the ease with which patent rights can be released, that is the government's rights can be waived. I see this frequently when we try to encourage private industry or developers to further extend new knowledge research results and get it out into the market.

In the past, you are exactly right that we would carry out the research and then hope that industry would step in. I think that now the Department is going much farther to try to accomplish a more effective interface for doing this and, as I mentioned, Los Alamos is specifically charged with doing this.

Senator BRYAN. Yes. And I would certainly encourage that and laud those efforts.

Share with me if you will just a little bit more of the specifics as to how that transfer occurs and who is involved. Assume for the sake of argument one of the national labs, one of the research projects that you are undertaking makes a significant breakthrough that would have some commercial application. Take me, if you will, very briefly from there. What are the policy guidelines? Who in effect has access to that new technology? Is it only American companies?

Can an enterprise from abroad, whatever the nationality of that company, get this technology?

Dr. Wood. Let me break it out into two areas. One would be data information, such as new findings, and publishable work and then the technology, including the new instrumentation and methodology.

Senator BRYAN. Okay.

Dr. Wood. Our view on this now is that the information, the data, that is published should be published as soon as the investigators are prepared.

Senator BRYAN. So, to interrupt, that is in the public domain.

Dr. Wood. That is in the public domain.

Senator BRYAN. Anybody that is capable of reading it can have it?

Dr. Wood. Peer review, journals, et cetera.

Senator BRYAN. Okay.

Dr. Wood. The technology is what we want to—if it looks like it is a step forward and if there are patent issues then we try to en-

courage—we first of all try to inform the private sector by a variety of means what these breakthroughs are.

Senator BRYAN. Okay, can I stop you there? When you say the private sector, that has some global implications as well. Are we talking about the private sector in the United States?

Dr. WOOD. The private sector in the United States, oh, yes. We want to involve them in the laboratories on joint projects to conduct a range of information transfer in this area by a variety of means. Perhaps one of the most effective is just personal contacts between our investigators in the laboratory and their counterparts, which is an effective way of accompanying this.

Senator BRYAN. For those items that are patentable, and I realize that is legal question as well, who owns the patent?

Dr. WOOD. Initially, I believe—I believe—that since the work is being performed at a nonprofit operated laboratory the contractor, the University of California has the first right to it. If the contractor for whatever reason, wishes not to pursue that, then the Government can acquire the patent rights or release them to the individual inventor himself.

Senator BRYAN. My time is up, but my last question is, assume it is patentable and the patent is owned by the Federal Government, assume it has potential commercial application and you have three or four companies that are capable of doing something with it. Does one company get exclusive rights? Is there a transfer of that patent ad hoc to Company X, or to Company Y and Company Z? Share with me very briefly, because my time is up and I do not want to encroach.

Dr. WOOD. I guess I do not really know, if there were four that came in at the same time and wanted to push it, exactly how the patent lawyers do that.

When they have one, they will look at the prospects that the company has, its track record, and determine whether or not it seems reasonable that they will be successful, in which they can give an exclusive or nonexclusive license to it and perhaps for a certain period of time.

Senator BRYAN. The bottom line is that we want our team, so to speak, to get any of the benefits of commercial applications arising from major breakthroughs.

Senator GORE. Senator Kerry.

OPENING STATEMENT BY SENATOR KERRY

Senator KERRY. Thank you, Mr. Chairman. Doctors, I join my colleagues in welcoming you and in expressing my sense of fascination with your testimony and with the prospects for what this project holds out for us. I think it is fair to say, and some have said it in different ways, perhaps, that this is perhaps one of the most extraordinary, exciting, challenging, and potentially majestic journeys that science has taken us on, with results that could be shattering in their ethical and disease-controlling and human consequences. I want to underscore what Senator Gore has said about ethics. While your answers to his questions are satisfying, at least publicly here, I still want to underscore it.

I think the myriad ethical, legal and social questions that are posed by this are beyond even our ability to lay them all out on the table now. In your answer to Senator Pressler, Dr. Watson, you talked about the capacity to make choices about what you do to treat one gene or another as you see early indicators of the potential for cancer. You indicated that the commercial aspects of this technology might conceivably be available and exploited to permit people to make other choices about the kinds of children they would bring into the world, that even governments may have that kind of selectivity is of enormous consequence to all of us.

So I think the issues are significant. Someone—I think it was in the "Science Magazine" editorial—wrote of the potential for abuses of commission. But there are also the abuses of omission which would come about by virtue of our not doing this and not availing ourselves of the opportunity to deal with the diseases that we have talked about and to reap the other benefits that could come from this.

So this hearing and this whole project really concerns an issue of the largest consequence. According to "Time" magazine, the Human Genome Initiative is on a par with the Manhattan Project and the Apollo exploration to the Moon. I think it is, indeed, all of those things and more.

Senator GORE. Would my colleague yield?

Senator KERRY. Sure.

Senator GORE. Just to elaborate very briefly on the examples that you're cited here, what about an insurance company, instead of using a very large risk pool, using very small risk pools and identifying the enhanced likelihood of a claim using information they demand from an applicant for insurance and adjusting rates accordingly?

At some point that is appropriate, but at some point it is inappropriate. We have no idea how to deal with those questions, and the people who are compiling the database which will provoke those questions have an obligation to help us develop a map of the ethics and the legal principles involved.

Another example: What if an employer has chemicals in the plant and finds that an applicant for a job has a 10 percent greater susceptibility to an occupational disease associated with exposure to that chemical?

At what point is the employer obligated to provide that warning? At what point is the employer justified in refusing employment on the basis, not of a genetic trait that is such as skin color, which is prohibited by law, but on the basis of a different kind of genetic trait that is part of that person's genetic heritage?

Again, our legal system, when confronted with such questions, shrugs its shoulders and says, we do not know. We have no idea. So again, as we compile the database we really have an obligation to look early on at these questions.

I appreciate my colleague yielding and will give extra time for that.

Senator KERRY. I applaud the Chairman's mentioning those particular examples, because I think that it is very, very important to understand the scope here.

While I think that scope is daunting because of the complexity and difficulty of some of the choices, I do not for an instant believe, as Dr. Watson and others have said, that this should restrain us from proceeding forward. Clearly, this is a journey we must proceed on with. It will benefit our Nation, opening up whole new horizons for improving our lifestyle, our health and so forth. So obviously, we must proceed.

This Initiative is going to be expensive and not uncomplicated. Whether it is going to take 15 years or longer, or less, we do not know yet.

The October 13 issue, of "Science" magazine, quotes a biologist as saying, "Jim Watson is trying to change the social fabric of science. It is World War II and directed science all over again." There are a number of concerns about the big science-little science issue: How are we going to come at this? Are centers really the entities best designed to do it? How will the peer review process work, and so forth?

Are some of those concerns and the skepticism that is being expressed being worked out, and are you confident that these centers are now proceeding in a way that the peer review process will be taken care of? Will there be adequate personnel to do the drudgery of the mapping work?

Dr. WATSON. Well, we have just put out our requests for the first centers. We hope to fund three in fiscal 1990 and as far as the quality of them, we just want a very distinguished group of peers to judge it, so I think it is very important the first ones we award are unassailable in the sense that no one can say it will not be money well spent.

I think, already, there are some forms of big science, if you look at the size of the laboratory of Bob Gallo at NIH, that is a big one, and I am glad it was big, because if we had not had a test for AIDS in the blood, the country would be in hysterics. So we do have big science now, and some of the issues just demand bigger groups, and some people are more suited to it.

You could say well, how can you compete if you are two people trying to develop an AIDS test versus a lab which has 50? Well, the answer is you probably cannot, but you probably should not be doing it. The country needs 50, so it is—really, if we want to get this job done and if you want to get the Alzheimer's gene in five years instead of 30, you are going to have to change the organization.

Now, we already have big, effective groups, and we did some marvelous things in World War II like the Manhattan Project. I mean, if there had not been the Manhattan Project there might have been many more American lives lost.

So I think if you believe in something you get the job done, and the fact that a few people want to persist in a style which is cost-ineffective, you know, if they were doing it in business they would go out of business and maybe in science they will not get their grant because someone can do it better because of better organization.

But we are limited for money. This program is not a WPA for people that want to go on there in a way which is not effective or efficient.

Senator KERRY. This subcommittee has heard considerable testimony in the past, doctor, about the shortage of both scientific and technical talent in the country. Is that going to be a problem for the Human Genome Initiative?

Dr. WATSON. No, it is not really that big. I mean, if you see it as 3 percent of the NIH budget. I think our main goal is to train people who can use computers so that when we get this information we are not going to waste an opportunity for our country to interpret it.

Senator KERRY. Dr. Wood, in the past, picking up on a theme which my colleague from Nevada has been stressing, the DOE has been criticized for not transferring technology to American companies. Do you have a plan in place, or an intention to guarantee that that story will be different with respect to the Human Genome Initiative?

Dr. WOOD. I am sort of repeating, but yes, we do have, through the laboratories, in place, specific programs that are charged with facilitating technology transfer between the national laboratory research effort and the American industry.

These are in place, they are moving forward and specifically in the genome area we are again trying to address that specifically. So we are trying to do what we can to try to assure that there is an effective transfer of technology.

Senator KERRY. How involved will commercial firms be in this process?

Dr. WATSON. I think we are going to be very involved with the companies that produce machines which sequence DNA, and the success of our program—you know, it is the thing "What is good for General Motors is good for the United States, or vice versa." Our program will be in trouble if our companies are in trouble. So they have to be involved.

Senator KERRY. Can you give us any sense of how the expenditures may divide up between commercial labs and the universities?

Dr. WATSON. I think it would be surprising if less than 10 percent of our money went to commercial firms and it could be a much larger percentage toward the end of the project, as we find out the most effective way to get the DNA sequencing done.

Senator KERRY. I met with a group of our biotech companies in Massachusetts recently, and one of the things that they complained about was how long it takes to move patents through the system now. They said that there is a real bottleneck and as a consequence nobody really knows who may have the rights to some particular process. Is that accurate, and is there any way to do something about that?

Dr. WATSON. You have to speed up the patent process.

Senator KERRY. How do we do that?

Dr. WATSON. Probably more examiners.

Senator KERRY. Are there enough examiners qualified to understand this area?

Dr. WATSON. No.

Senator KERRY. So what do we do?

Dr. WATSON. Commercially, you would say raise their salary and more people will go into it, but I do not know quite how to do this within the—

Senator KERRY. You are indeed a replacement for Ronald Reagan.

We will just add it to the debt, right?

Senator GORE. If I could interject, I have been hearing the same message, Senator Kerry. This is one of the main bottlenecks, and we have really got to solve it. I would be delighted to join with my colleagues on this subcommittee in initiating communication with the sister committees that have jurisdiction over the Patent Office to advise them that in our investigation in this matter we have once again identified this as a major concern and attempt to speed up a solution to it.

Senator KERRY. I agree, and I will join in that effort with others, because my constituents expressed a deep concern about these delays. This is a real problem to them and it is slowing down the process of commercializing. This it is one more instance in which we seem to shoot ourselves in the foot with respect to our own productivity and commercialization.

What are the major barriers that you see to the commercialization of the new technology within this field?

Dr. WATSON. I am not—probably capital.

Senator KERRY. Truly, capital?

Dr. WATSON. Yes, capital.

Senator KERRY. Dr. Wood.

Dr. WOOD. I think, as we were talking earlier, I look at this as three stages, if you will: the research stage, which we handle very well, the other end is the marketing stage, and then there is this interface or coupling between the research side and the marketing end of it. The latter is an area that we have really got to work on because I think that it is toughest to get this technology through to the private sector and that is what we are trying to do. I think we have to go about it in as many innovative ways as we can think of to effectively accomplish that transfer.

Senator KERRY. I know my time is up, and I also have to go to another committee briefly, but I am going to try to get back. Let me just say I thank you to both of you for your participation. I look forward to working with you.

Mr. Chairman.

Senator GORE. Thank you, Senator Kerry. I have a couple of follow-up questions and if my colleagues wish to ask a comparable number they will certainly have the opportunity to do that.

I wanted to explore very briefly with you, Dr. Watson, this question that Senator Bryan asked which you deferred to Dr. Collins. We will pursue it with Dr. Collins also, just how practical is it to retain proprietary control over information that describes the common heritage of humankind?

If the information is published as part of research into various aspects of the genome, and if it is available throughout the research community, how practical is it to retain ownership of such data?

Dr. WATSON. Well, I will put it this way: you look at a DNA sequence and—you look at that and that smells like a polypeptide hormone and maybe that would be a good painkiller. So if you were a drug company you would get that sequence translated to

protein and see if it works. So you really just—you have to see a use to the sequence.

But I am not a lawyer—I am not a patent lawyer, but you really have to—you just cannot patent it, *per se*. You have got to be able to use that information and say, from that we have an idea for a potential drug and we go and get the drug.

Senator GORE. Here I am backing away from the patent discussion and homing in on your proposal to withhold data from the Japanese. I do not quarrel with the logic of your proposal, but I am wondering how practical it is.

Dr. WATSON. I will come back to the point that the people who are doing the sequencing may want to have a first round of looking at it. And you can say, should they have a year? Should they have two years? Should they have three years?

Senator GORE. What do you think?

Dr. WATSON. If I got something in return—

Senator GORE. What if you do not? What if you do not? How long should you have it and how long could you have it, as a practical matter?

Dr. WATSON. See, up to now when we have gotten data—they did a very interesting sequence of the DNA of chloroplast in Japan, and they published it.

But they did not publish it before they had really said these are all the genes and assigned functions to a number of them. And then the paper came out. And they got the credit for a very nice piece of science.

So I think we would not want to distribute the data, until we looked and saw the genes and said these are the genes. That would be—because people are going to do it, in part, because they are scientists.

And, so, I think this is a very difficult issue. But there are people who would say that even before anyone begins to interpret the data, we should put it in a database so anyone in the world can do it. Because that will speed up science, and that will be good for the world. That is one argument.

The other argument is that—or two others: it is commercially valuable or, second, that the people who have done it want some scientific sense of achievement.

And we are going to talk about this for many years to come.

Senator GORE. Indeed. Do you have a view on this Dr. Wood?

Dr. WOOD. I think if there is a clear commercial potential, we have to take every effort we can to make sure we couple that with the American industry.

But, as I said earlier, data, publishable information, I personally feel that that should get out into the public literature, the public domain.

Senator GORE. Do you have a disagreement on this?

Dr. WATSON. No, I—

Senator GORE. It sounds like you do a little bit?

Dr. WATSON. Well, he said publish. But, you see, after you have published it, that is, after you have said something about the data. You are not just passing out letters that you have not tried to look at.

Senator GORE. Do you think there is a difference, Dr. Wood?

Dr. WOOD. I am not really sure whether we have a difference on this one or not. I am looking at it from—when information gets to the point where it is publishable, recognized as such by the peer reviewers that it has go to through, that we should move that forward as quickly as possible and get it out so that other scientists have it are available.

Senator GORE. Even before you take a year to play around with it?

Dr. WOOD. If it is suitable to be published. Now, if you recognize the commercial potential in there, then, I think we want to take that part of it and try to move it into the American industrial sector.

And I do not think there is a clear answer on this.

Senator GORE. Evidently not.

Dr. WATSON, that sounds different from what you said to me?

Dr. WATSON. I want to look at it and see if I can spot the genes and identify them and say what they mean. And now, you may fail. You have a bunch of sequence you have—

Senator GORE. Well, they can be publishable. It can be suitable for publication before you complete that.

Dr. WATSON. I mean, you can just pass it out on a desk for anyone to interpret it. And that would be one scheme.

Senator GORE. That sounds like your scheme, Dr. Wood.

Dr. WOOD. Well, and I think that the—

Senator GORE. Was that a yes?

Dr. WOOD. Yes.

Senator GORE. Okay. But, Dr. Watson, you do not agree with that approach?

Dr. WATSON. No, not for right away. I want to look at it, because I am a scientist.

Senator GORE. Well, who is going to decide which approach is taken? There is an empty chair there between you.

Is that who is going to make the decision?

Dr. WATSON. I think there is going to be some horse trading. If you can get something in return, you are going to give it. If you do not get anything in return—

Senator GORE. How many base pairs in a horse?

Dr. WATSON. Well, about the same number as in a human. And—

Senator GORE. All right. Well, this is one of the questions you will have to wrestle with in completing your joint memorandum. Correct?

Dr. WATSON. It is not a real issue now, because we do not have the data to pass out. Five years from now it is going to be a very real issue.

So, I think about all we can do now, is to point out the alternatives. But I do not think there would be enough convergence to a common opinion that it would make any sense.

And I would also really hope that the HUGO can get going, and, then we can have discussions on a sort of worldwide level. I mean I really—

Senator GORE. But the Japanese have not provided much funding compared to us.

Dr. WATSON. The sums of money we have suggested be given to HUGO are so trivial compared to the, you know, the—just ask yourself, what the profits of Toyota are per year. Much, much greater than what they use to support science in Japan.

Senator GORE. Are you impressed at all with the recent genome mapping starts in Japan? There have been a few small projects started recently. How do you evaluate them?

Dr. WATSON. I am not scared.

Senator GORE. All right.

We need several of you, Dr. Watson, in robotics and autos.

Where does the Human Genome Initiative fall on the list of priorities at NIH, compared to AIDS, cancer, et cetera?

Dr. WATSON. I think for that answer you have to have a director of NIH appointed.

Senator GORE. You are pretty good at this game, too, Dr. Watson.

How will this joint research plan be prepared? Just how are these differences going to be sorted out?

Dr. WATSON. There is a draft. It has been sent to—the draft was prepared by my office. It went to the DOE. They have made suggestions. It is going back and forth. We are going to present it to our joint advisory committees in early December.

Senator GORE. Could we see it?

Dr. WATSON. Yes. Sure. By that time, you can certainly see it.

Senator GORE. Can we see it now?

Dr. WATSON. Yes. I would have no objection.

Senator GORE. Great, we will talk to you after the hearing.

Now, you talked about sequencing some small genomes before doing the human genome.

What do you propose to start with? E. Coli? Some other bacteria?

Dr. WATSON. We have a grant to the University of Wisconsin for a big E. coli project. And there is an—

Senator GORE. E. coli has about 4 million or 5 million base pairs, as compared to 3 billion base pairs in humans.

Dr. WATSON. Million, yes.

Senator GORE. Nothing complicated like the lilies of the field with 90 billion.

Dr. WATSON. Actually we have about five applications. Two are for bacteria, one which would be done jointly with people in the U.K., for the worm *C. elegans*, and then there would be an application from Dr. Hood, which I do not know whether it would be funded but we are getting the application, to work on the T-cell receptor. That is a human sequence.

And, then, there is one for a section of the X chromosome, with Dr. Ventor at NIH working with Dr. Caskey at Baylor.

So we may be doing two human sequencing projects. So, we are—and you choose the human from those which you think are medically interesting. So, we are not trying to sequence junk. We are trying to get something useful.

Senator GORE. Senator Bryan.

Senator BRYAN. Thank you, Mr. Chairman.

I certainly applaud your holding these hearings. I would hope that we might, as this evolves, have some subsequent follow-up hearings concerning what kind of progress is being made and

where we need to go. And whether the Congress needs to provide any direction.

Let me just ask one question, because I know we are going to be called for a vote very shortly.

Dr. Wood, I invite your candor, if I may, of the unvarnished variety.

You indicated, in response to a question that Senator Kerry asked you, that we do very well on the research side.

You did not say it, but I think it is self-evident that we do not do very well on the marketing side at all, and that, as you see it, that we need to couple those two and strengthen our ability to move from research to the marketing side.

Now, that was certainly the thrust of my questions during my last opportunity for questions. You were both asked about barriers to commercialization. I think Dr. Watson said capital was his response.

Share with me, from a government perspective, the frustrations which I know you must have with the private sector. Let's assume that you have brought this new energized, enthusiastic, cooperative attitude to DOE to try to accelerate the transfer of technology. What is the private sector not doing in terms of interfacing with DOE to expedite that transfer?

Dr. Wood. Perhaps capital is the answer. But what we have seen is that they are asking us to go further and further in terms of developing a particular instrument or a particular capability. In our instrumentation program, not necessarily the genome program, we would develop a new instrument to the point where we had demonstrated its feasibility, and that it is an advance. Perhaps it would be picked up in our national labs, in their instrumentation shops.

And, then, we would tend to stop that development in the anticipation that industry would come forward to do the marketing. By that I mean the manufacturing—the further development of the instrumentation until it becomes a standardized product.

We would hope that that happens. That has happened. But we also see an effort on the part of much of an industry, to have us to go further and further along that chain of development what is eventually a marketable item.

The question of how far along we should go is where the difficulties are. They want, the government, to put more money into a particular device to bring it closer to being a marketable item.

Senator BRYAN. So, the private sector is failing, in effect, to seize the initiative?

Dr. Wood. Exactly.

Senator BRYAN. You have got a raw technology that has enormous potential, and they are saying, "Hey look, you all spend some more money, perfect it, and we will wait for you."

Dr. Wood. Yes. We have encountered that attitude. Yes, indeed.

Senator BRYAN. And I suppose some of that maybe does relate back to Dr. Watson's observation—capital—it costs money to do that, to develop it and market it.

Anything else, Dr. Wood, that you see from your perspective?

Dr. Wood. No, I think that is the one key issue that I have found.

Senator BRYAN. Can you give us some sense of whether we are doing a little better in terms of that interfacing? Have you been able to energize the private sector and get them fired up a little bit more? Or do you see them still—

Dr. WOOD. No, I think we are trying to do that. We are trying to deliberately interface more effectively than we have in the past.

Senator BRYAN. Sure, now you have indicated that previously in your testimony. I think all of us on the subcommittee appreciate it.

I'd like to know more about the private sector reaction. Is there a sense of urgency? This global marketplace out there is pretty damn competitive. And 1992 will bring additional competitive pressures from Europe. Our market share of this new technology will be much smaller or perhaps nonexistent, if we do not get folks fired up.

Do you sense that the private sector comprehends that and is willing to do something about it?

Dr. WOOD. Certainly in our interface with the bio-technology community, we sense that.

Senator BRYAN. Well, that is good news. And I hope you will be an advocate and a cheerleader for those efforts.

Mr. Chairman, I thank you. And now we have got to go cast a vote here very shortly.

Senator GORE. Thank you. Let me thank both of you for your excellent testimony here today. We really appreciate it. Thank you so much, and good luck in your continuing efforts.

Let me invite our second and final panel to come to the witness table.

Dr. Francis Collins, Ms. Patricia King, Dr. Maynard Olson and Dr. Nancy Wexler. As you are making your way to the witness table, let me formally introduce and identify you by title.

Dr. Francis S. Collins is Associate Professor of Internal Medicine and Human Genetics at the University of Michigan Medical School in Ann Arbor. Welcome.

Ms. Patricia King is Professor of Law at Georgetown University Law Center here in Washington. Welcome.

Dr. Maynard Olson is Professor of Genetics at Washington University School of Medicine in St. Louis.

And Dr. Nancy Wexler is Associate Professor of Clinical Neuropsychology at the Departments of Neurology and Psychiatry at Columbia University in New York.

Welcome to all of you. Delighted that you could come and join us here today.

As Senator Bryan noted, we have a vote that is imminent on the floor of the Senate. Sometimes we are told a vote is imminent, even though it is not, so we will start and go as far as we can. But I anticipate the bells will ring momentarily.

So, Dr. Collins, if we have to interrupt part-way through your presentation, we will do so. But why do you not go ahead and begin?

Welcome.

STATEMENT OF FRANCIS S. COLLINS, ASSOCIATE PROFESSOR OF
INTERNAL MEDICINE AND HUMAN GENETICS, UNIVERSITY OF
MICHIGAN MEDICAL SCHOOL

Dr. COLLINS. Thank you. I will try to keep my remarks brief, because I want to give everybody a chance to speak.

My research group, working together with a group at the Hospital for Sick Children in Toronto, was recently successful in identifying the gene for cystic fibrosis (CF). I might add that this was a nice example of an international collaboration that worked very well.

I suspect the reason I am here is to comment on the steps involved in cloning the CF gene, and what consequences the human genome project holds for future gene identifications of this sort.

Finding the CF gene can be compared to trying to identify a single burned-out light bulb in a house somewhere between New York and Los Angeles, without having ahead of time a map of the area.

And that, as you can imagine, was a bit of a laborious task. And it took a number of years, and a lot of hard work, and a lot of money.

In effect, we finally succeeded through a process of narrowing down the area of interest to the right state, to the right town, finally to the right house, and then finding the right light bulb in that house.

And that is the sort of process that will need to be carried out to find other genes for diseases, such as Alzheimer's Disease, which has been mentioned, or for schizophrenia. It should even be possible for genes which cause relatively common disorders, such as diabetes, heart disease, breast cancer, all of which have a major genetic component.

The conditions that I just listed, however, probably will not be approachable without the human genome project. They are, in fact, much harder problems. As hard as CF was, by comparison to some of these other disorders, it was an easy one. This is because it is a single-gene disorder, it is inherited in a genetic fashion that is very predictable, and there are a lot of families available for study, because it is relatively common.

That will not be so easy for a variety of other problems. We will do very well indeed with other genes such as Alzheimer's disease to narrow down our candidate area to a region that contains less than 100 genes. To have to search through such a large region without a map, without knowing where the swamps and the cliffs and the mountain ranges are, is probably too difficult for current scientific effort to achieve.

On the other hand, if the human genome project were completed right now, these diseases would be approachable and would likely yield success in the not-too-distant future.

I am a practicing physician; I regularly care for patients with genetic diseases. I am acquainted with the frustration, suffering, and human tragedy brought on by these devastating disorders. The hope for those individuals and the long-term future of medicine rests with the success of this project.

If we do not go forward vigorously with this effort, we will have a rather short list of diseases like CF where we have been successful, and a very long list that continue to be puzzling and unattainable.

So, even though it is a difficult and expensive effort, I think the human genome project is the way to move bio-medical science into the 21st century. It will change the face of biology, and drive our entire medical establishment rapidly forward, I am quite sure, by its spin-offs. Not to move forward at this point would be a terrible mistake.

[The statement follows:]

Implications of the Human Genome Project for the Future of Medicine
 Testimony on the Human Genome Project
 Francis S. Collins, M.D., Ph.D.
 University of Michigan
 November 9, 1989

Senator Gore and members of the Subcommittee on Science,
 Technology and Space:

It is an honor and a privilege to come before this committee to share my views about the Human Genome Project, and its implications for the future of clinical medicine. Our recent success in cloning the cystic fibrosis gene, in collaboration with a research group at the Hospital for Sick Children in Toronto, has led to increased excitement about the use of similar strategies to identify other genetic components of disease. Certainly the Human Genome Project promises to greatly facilitate such efforts, which may be otherwise difficult to generalize.

Cloning the cystic fibrosis gene: What was done

Cystic fibrosis (CF) is a genetic disease inherited in a recessive fashion which affects 1 in 2500 newborns. One in 25 Caucasians is a carrier for this disorder, and when two carriers mate, there is a one in four chance that a child of theirs will be affected. The disease has pronounced effects on the digestive system, where the pancreas fails to secrete digestive enzymes properly and malnutrition is a result, though recent improvements in enzyme replacement have made this part of the disease more manageable. The major morbidity of the disease relates to its effects on the lungs. The mucus produced in the airways is thick

and sticky, and tends to block the respiratory tree, leading to chronic infections and destruction of the lungs. A person today with CF has only a 50% chance of living to age 25, in spite of considerable improvements in outlook based on antibiotics and physical therapy. Decades of research have failed to uncover the basic defect in cystic fibrosis, except to indicate some problem in the transport of ions, particularly chloride, in affected tissues. Thus, the standard biochemical approach to understanding a disease, which is referred to as "forward genetics", has failed in CF. Unfortunately, the vast majority of genetic diseases which affect mankind fall into this same category; there is simply not enough information available to deduce the mechanism of the disease. Until recently, it was unclear that such diseases could ever be understood.

Recently, a new strategy, called "reverse genetics", has emerged which holds great promise for the identification of such genes. This has now been successfully applied for cystic fibrosis, as well as for four other diseases, including muscular dystrophy.

The starting point of reverse genetics is to map the disease gene to a specific human chromosome by following its inheritance in families. Using genetic analysis, it is then possible to narrow down the region on the chromosome where the gene must lie, reducing the area that needs to be considered in the most optimum circumstances to a region which includes on the order of 30 or 40 genes. At that point, the search becomes difficult, as a very

large amount of DNA must be investigated, and it is very challenging to decide when the right gene has been identified. In general, proof rests upon identification of abnormalities (mutations) in the gene in patients with the disease.

To render this situation more understandable in every day terms, one can think of the search for the cystic fibrosis gene as analogous to trying to identify a single burned out light bulb in a house located somewhere between New York and Los Angeles. Prior to 1985, there was no information whatsoever about where one should look for the CF gene. In 1985, family analysis located the CF gene to chromosome 7, which is analogous to defining which state the house with the burned out light bulb must be located in. A year after that, the region of chromosome 7 had been narrowed to about 1% of its length, which is similar to identifying the right town in which to focus the search. Over the past three years, working closely together, our group at the University of Michigan and the group at the Hospital for Sick Children in Toronto have been performing a house to house search in that town, using a variety of new technologies to speed up the effort. One of these, called chromosome jumping, enabled us to effectively leap from street corner to street corner and initiate new searches simultaneously from several startpoints, rather than having to travel in one slow continuous walk from one end of the town to the other. By last spring, we had identified a house which looked suspicious. Only after investigating all of the light bulbs in the house, however, did we identify one which represented the true abnormality. In the

case of cystic fibrosis, the burned out light bulb was a very subtle one; if you will, you can think of it as a night light, not a floodlight, and this added to the challenge of the task.

In achieving this goal, we stood on the shoulders of many individuals who have prepared the way, particularly those who recognized nearly a decade ago that we needed a genetic map of all the human chromosomes in order to carry out such work. This time consuming effort has provided a series of landmarks to make it possible to at least approach the problem. However, the current map is quite crude relative to what one would really like. As detailed below, this is a great motivation to undertake the Human Genome Project. One of the difficulties in identifying the cystic fibrosis gene was the absence of good maps to tell us where the states, towns, houses, and light bulbs were. Having to build the map as you go along makes the whole task enormously more difficult than it otherwise would be.

The cystic fibrosis gene search was very expensive. The Cystic Fibrosis Foundation alone spent some \$200 million over the course of the last ten years encouraging scientists towards this goal, and at least this amount has been spent by the National Institutes of Health, as well as a sizable amount by the Howard Hughes Medical Institute and other supporting groups. Though the task was enormously difficult, one could argue that identifying CF was in fact one of the easy ones, for the simple reason that this is a common disease where many families are affected and the

diagnosis is unequivocal. This makes the genetic mapping much more powerful, because so many genetic events are available to be studied. For diseases which are less common, or for which the inheritance is less clear cut, the task becomes markedly more difficult.

Can reverse genetics be accomplished for other diseases? How will the Human Genome project assist the search?

There are a large number of disorders whose genes are being sought by this approach. Examples include neurofibromatosis, Huntington disease, polycystic kidney disease, and familial colon cancer. It is likely that at least some of these genes will be found in the relatively near future, prior to the full achievement of the scientific benefits anticipated from the Human Genome Project. However, with the current limited arsenal of technology and genome information, the list of successes will be relatively short.

As noted above, the "reverse genetics" effort is most successful when the disease is very well defined genetically. As an example where the problem is much tougher, consider Alzheimer's disease, a major cause of morbidity, human suffering, and health care expenditures in our country. A major genetic component to Alzheimer's disease has been defined in many studies; in some families where the disease incidence is quite high, a gene responsible for susceptibility has been mapped to chromosome 21. Genetic mapping is difficult, however, because in some families the

inheritance pattern is not clear, and the late onset makes it very difficult to obtain families in which multiple generations are alive with the disease. For these reasons, it is almost impossible to narrow the region of the Alzheimer gene to less than 5% of chromosome 21. Such an interval is large enough to contain as many as 100 genes. Even recent advances in technology, some of which were utilized in the CF gene search, are not really up to the task of solving such a difficult problem.

If, on the other hand, the Human Genome Project had already been accomplished, the entire map and DNA sequence of this region of chromosome 21 would already be known. The DNA sequence could be analyzed, especially with the help of DNA sequences from other species such as the mouse, to identify the location of most of the genes in this interval, using computer analysis. Since DNA contains all of the information necessary to predict the sequence of an encoded protein, those predicted proteins could be studied and compared to other proteins of known sequence to deduce some information about the possible functions of a reasonable fraction of the genes represented in this interval. With the known sequence in hand, it would also be possible to directly look for differences in the sequence of these genes in individuals with Alzheimer's disease. The task would still be challenging, in that a rather broad search would have to be initiated. However, with the normal mapping and sequencing having been carried out, the task would be imaginable; at the present time, it may not be so. Returning to the analogy given above, one can imagine how much easier the task

of finding the appropriate burned out light bulb would be, if ahead of time you are given a complete map of the towns, a listing of all the houses, and the location of all the light bulbs. If, on the other hand, you are forced to build your own map as you go along, often working in the thick fog, the results are less predictable.

Another daunting challenge for the future is the mapping of genes which are responsible for predisposition to more common diseases which are not inherited in a simple genetic fashion. This includes such disorders as cancer, coronary artery disease, diabetes, and psychiatric diseases. Methods are now being developed to analyze very large families with a higher than usual incidence of such disorders, and to simultaneously identify several general regions of chromosomes which contribute to the risk of such disorders. However, the mapping will not be tightly localized, so that the eventual identification of such critically important genes will come down to a search through several large regions. Here again the prospects of success seem dim unless the Human Genome Project goes forward. One cannot predict ahead of time which chromosomes or regions of chromosomes will harbor important predisposing genes, which is another argument that one must simply do the entire Human Genome.

Implications for clinical medicine

Thus, as described above, the Human Genome Project should provide the basic tools necessary to greatly facilitate the mapping

of a large number of genes responsible for human disease. While the implications of this for the clinical practice of medicine will not be felt overnight, in the long run the effects are likely to be far-reaching, and to have a significant positive impact on health.

Identification of genes which cause human disease will have their most immediate impact in the short run on diagnosis. Identification of the CF gene and its most common mutation, for instance, now makes possible testing of individuals with no family history of this disease to find out if they are carriers. This will for the first time permit couples at risk for having an affected child to know this information prior to starting their families. This sort of genetic screening raises a number of ethical and legal issues which need careful consideration, though they are not entirely new. One of the basic principles of Medical Genetics is that the individual directly involved should have the right to decide whether he wants such information, and that the decision about what to do with the outcome of the test rests solely with the individual being tested, and not with his physician, his insurance agent, his employer, or other members of society.

I should point out, however, that the real goal of the identification of human disease genes is not simply diagnosis but also treatment. A clear example of the effective treatment of genetic disorders is the disease phenylketonuria (PKU). Untreated children with PKU become profoundly retarded, but early identification of the disease, which is now carried out by newborn

screening in all states, allows the institution of a special diet which leads to normal functioning and a normal life span. While such dietary treatments are unlikely to be possible for many genetic diseases, the identification of the responsible gene may be the first step to the development of effective drug therapy, or even of gene therapy, where a correction of the problem is carried out at the DNA level.

Identification of genes responsible for predisposition to common diseases will also have very important consequences for preventive medicine. A woman known to be at high genetic risk for breast cancer, for example, could be strongly encouraged to learn self-examination, and to undergo screening exams such as mammography on a very regular basis, as we know that early detection of tumors correlates with survival. Similarly, a person at high risk for colon cancer could be given the option of intensive surveillance for the development of tumors. An individual found to be at high genetic risk for heart disease might well be more motivated to follow a sensible diet and avoid cigarette smoking. In effect, the identification of such genes, while sounding revolutionary, is not different in principle than what is currently done in obtaining a serum cholesterol, which also is a useful predictor of heart disease. The difference will be in scale; a much broader range of conditions will be predictable, and with a higher accuracy.

In summary, the Human Genome Project is probably the only way that the full power of the revolution in modern genetics can be harnessed towards identification of the basic causes of the diseases which haunt our species. To carry out this task piecemeal as a cottage industry, as in effect we did for cystic fibrosis, will soon inhibit the process and run the risk that many of the most important targets will never be reached. We have a unique opportunity in the United States to coordinate the resources and the talents to achieve this goal. The resulting wealth of information is likely to become the driving force in biomedicine in the 21st century. In my view, the Human Genome Project is the most exciting challenge in medical science in the coming decades. While there are important ethical and legal implications which need to be investigated, I am convinced that with careful discussion those hurdles can be negotiated. We owe it to ourselves and to future generations to pursue this information. It is too fundamental, too central to life, too crucial to the future of medicine, and too essential to understanding the mystery of our creation, to let such an opportunity pass by.

Senator GORE. Do you want to discuss the question Dr. Watson anticipated you would discuss?

Dr. COLLINS. Dr. Watson has more faith in me perhaps than he should. And I take that as a great compliment, considering where it is coming from.

One of the issues that he deferred to me was the business of patenting. Is, in fact, patenting of a human DNA sequence likely to hold up? And I have to say from the outset that I am no more a lawyer than he is.

My understanding of this is that most patent lawyers feel that, if you have a sequence which can be used in a particular way, that that use is, in fact, patentable. Therefore, our respective institutions, Michigan and Toronto, have in fact filed a patent to cover the common mutation which is present in cystic fibrosis, as well as the normal gene sequence around it. This was done with the anticipation that many companies will become interested in the possibility of providing genetic screening tests for CF, since one in 25 caucasians in the United States carry this mutation.

It is my understanding that this patent is likely to be issued. I certainly echo the concerns about how slow the patent process is, because it has been quite confusing for companies who now want to start down this path to know where they stand.

So, I think, there is a legal basis for what is being done.

Senator GORE. All right. We will pursue that in questions.

Professor King, welcome. Your statement will also be in the record, please proceed.

**STATEMENT OF PATRICIA A. KING, PROFESSOR OF LAW,
GEORGETOWN UNIVERSITY LAW CENTER**

Ms. KING. I will try and be very brief. I would like to first say that I am a member of the working subcommittee to the genome initiative project, but I am not testifying in that capacity. I am testifying as a private individual. And I will not speak for the working group. Dr. Wexler will do that.

I would also like to say in light of previous comments that I am not a patent attorney.

It seems to me that the ethical issues, and I think ethical issues are social issues at bottom, are extraordinarily significant in connection with the genome initiative.

I will not say they are more significant than the scientific work, but surely as important as the scientific work. And I would also point out that many of the issues raised by the human genome project are not new issues, not new ethical issues.

Many of them are ethical issues that have already been created by past advances in medicine and science. So, I see, at least for the foreseeable future, at least until we start identifying new ethical issues, that for the foreseeable future our task will be to attempt some resolution of issues that have already been identified.

Resolution may involve several different kinds of things. For some issues it seems to me we may not have enough data. For example, we know far too little about the clinical provision of genetic services.

We are beginning to learn something, but we need to know a great deal more. Some of these issues will require creating new mechanisms to resolve the issue, new mechanisms particularly for involving the public in the ongoing discussion. The past election results to the contrary, I for example think that, the increased use of focus groups and polling to help us identify how the public's values and public's feelings in this area are going to be very important.

I also think that in resolving some of these issues that, while NIH is going to take the lead and be the primary spokesperson, spokes-institution, for some of these issues, that social issues go well beyond, it seems to me, what NIH has done particularly well in the past. It seems to me that they will be able to handle many of the research efforts.

But resolution is going to require legislation in some of these areas. Insurance, I identify, as one of those areas where we are probably going to need some legislation. And resolution will require probably a broader constituency than NIH currently has.

That to one side, I certainly think that NIH is the logical spot to lodge a mechanism for focusing on some of the social and ethical issues.

I think I will stop there. I have tons of examples to say that the issue is resolution rather than identification. But I will wait for questions.

[The statement follows:]

Testimony Before Senate Committee on Commerce,
Science, and Transportation
Subcommittee On
Science, Technology, and Space

Patricia A. King
Professor of Law
Georgetown University Law Center

My name is Patricia King. I am a Professor of Law at Georgetown University Law Center. I appreciate the opportunity to testify before you today on the ethical and public policy implications of the human genome initiative.

Societal approval, evidenced by governmental funding, for the mapping and sequencing of the human genome is grounded in the assumption that information obtained through such efforts will be beneficial to individuals and society in general. Some clearly question this assumption. For example, they worry that too much emphasis will be placed on knowledge of one's genes to the detriment of other factors such as the environment on human development and well being. Others worry that too much effort is being devoted to producing situations where diagnosis but not treatment or amelioration of human genetic disease will be available. They also worry that society may fail to develop such therapeutic measures in the future if abortion remains an available option. Despite these and other misgivings, I believe that many more people accept the assumption that mapping and sequencing the human genome is potentially very beneficial but they worry about the ways in which the information produced by these efforts might be misused.

This concern is not without foundation. The legacy of the eugenics and racial hygiene movements continues to cast a long shadow over current discussion of human genetic research. Genetic arguments have historically been used to justify the superiority of one group over another. Practices carried out in Nazi Germany come immediately to mind. But I cannot forget that the eugenics movement was very active in this country near the turn of the century. During that period the Supreme Court held that the Constitution permitted sterilization of persons who were mentally disabled. In the words of Justice Oliver Wendell Holmes, "three generations of imbeciles are enough." Justice Holmes wrote those words in *Buck v. Bell* -- a case that is still good law because it has never been overruled. Moreover, mandatory sterilization statutes are still on the books in some states. Antimiscegenation statutes and racially discriminatory immigration policies are other examples of public policies that were premised on the superiority of certain races. More recently, individuals, African Americans in particular, have suffered discriminatory treatment in employment and in insurance after being identified as carriers of genetic traits or as suffering from the genetic disease.

In response to concern about the possible misuse of information obtained through the human genome initiative, the Office of Human Genome Research [National Center for Human Genome Research] has announced its intention to spend between 1% and 3% of its budget on exploring social, legal and ethical issues. NIH

is to be commended for this commitment of resources. To my knowledge this is the first time in our history that we have acknowledged that scientific efforts generate significant social and ethical issues that must be explored, and hopefully resolved, before the basic scientific work is completed. It may be the case, however, that over time it will become necessary to put additional resources into this effort. In my view, understanding and resolving the ethical, legal and social implications of the human genome initiative is every bit as important as the basic science itself. This effort, moreover, may prove to be more costly than anticipated if we are to do it well.

Much effort has already been expended on the identification at a general level of the many legal, ethical and social problems that the genome initiative might generate. Some assume that these issues are new and frightening. I disagree. While there will undoubtedly be new issues that we have not encountered before, I suspect that the ethical and social issues have numerous precedents. I believe that we are dealing with variations on themes encountered earlier in the area of genetic screening and counseling or other areas of medicine such as in the diagnosis and care of patients with hiv infection. What is different is that new and more efficient techniques will yield more and better information. The issues will have changed only to the extent that the magnitude of the problems encountered will be substantially greater. For example, selective termination of fetuses has been a troublesome issue for some time. Not only do

some have concerns about abortion in general, but others question whether abortion following identification of a fetus with a genetic disease sends the wrong message to disabled people and society about the worth of lives with impairments. Information from the genome initiative is likely to increase the magnitude of this issue and hopefully push us to some resolution. It should be possible to be committed to access and choice for parents and at the same time not present abortion as the only realistic option. Society should provide support for those parents who do not wish to abort but who need assistance in meeting the needs of their disabled children.

Hopefully, the sheer magnitude of the ethical and social problems will make it imperative for society to tackle in a meaningful way the issues generated, but not resolved, by earlier technological and medical advances. With determination and adequate resources and the momentum from the genome initiative perhaps adequate policies can be formulated that will minimize the potential for misuse of information about the genetic composition of human beings.

What then remains to be done so that we can begin to formulate public policy concerning uses of information acquired from the genome initiative? Some of the remaining work is conceptual in nature. Much more of the work will be empirical. Finally, we need to devise mechanisms for resolving the conflicting and competing values at work in these ethical issues and to attempt resolution of these issues in a manner consistent

with practical realities, such as limited resources. It is critical with respect to this latter effort that work out ways to understand better the public's concerns and values.

Understanding and appreciating the public's views is important not only in helping to formulate the policy agenda but also because the public must be educated and provided meaningful information about developments in human genetics. Let me elaborate further on the work that remains.

One of the issues most frequently raised in connection with the genome initiative is what impact better information will have on our system of insurance. Put succinctly, should insurance companies have access to genetic information about individuals? If information is used for the purpose of denying insurance, are such practices permissible ways of differentiating among individuals? My intuitive response to this problem is that insurance companies should be denied access to such information.

This is not a new issue. Insurance is a device for reducing risk by combining individual exposures in order to make individual losses collectively predictable.¹ Risk in the insurance context is understood to mean uncertainty concerning loss. If the future is perfectly known there is no risk and no need for insurance. As Mehr, Cammack and Rose point out, "[i]f it is known that something will or will not occur, no uncertainty

¹. The following information about insurance was taken from Mehr, Cammack and Rose, Principles of Insurance, 8th Ed. (1985) as excerpted in Keeton, Keeton, Sargentich & Steiner, Cases and Materials on Tort and Accident Law, 2nd Ed. (1989), pp. 459-465.

prevails and hence no risk. The inability to predict the course of future events is the essence of risk. And as events become more predictable, risk is reduced. Risk makes insurance both desirable and possible. If in a given case a loss were certain to occur, insurance could not be obtained."

Insurance companies have always attempted to eliminate the known loss. They have required medical examinations before issuing coverage. They have refused to cover, or have covered only partially, costs attributable to pre-existing conditions. Where insurance companies have issued policies to persons with known risks, they have often charged higher premiums. While it is the case that insurance companies have not in recent times been permitted to use gender or race-linked indicators, we should bear in mind that gender, race and ethnic group are not highly accurate proxies for individual risks. Insurance was thus viewed as a mechanism for the individual to secure the individual's future -- an extension of responsibility for self -- not as a means of assistance to those who were disadvantaged in some way. The result of utilizing these practices -- practices albeit consistent with our theory of insurance -- has been to burden those most in need of assistance.

These views are changing. As a result of the spread of hiv infection and the enormous costs involved in the care of infected persons, many have started to question the long accepted practices of insurance companies to eliminate known losses from coverage. Parallel with the increase in awareness about hiv

infection and its consequences has come new understanding of physical and mental disabilities. More and more we have consciously moved to bring individuals with mental and physical disabilities into the mainstream of society. This trend has been given new momentum by knowledge that individuals may have impairments that will not become symptomatic for long periods of time.

A means of resolving this conflict is to prohibit discrimination against individuals on the basis of genetic disability, including those individuals who are asymptomatic.² In my view an individual's draw in the genetic lottery is closely analogous to characteristics of race and sex. These are all characteristics beyond the power of individuals to control.

We do need to consider carefully, however, the appropriate framework for this policy. For example, should differential treatment on the basis of genetic disabilities almost always be discrimination (race); nearly always discrimination (sex) or should we chart a new course for genetic disability all together?

Even if differential treatment on the basis of genetic disability is prohibited, the question remains about how to provide support to individuals who are unlucky in the genetic lottery. Answers to this problem might require rethinking insurance assumptions. Such efforts could also require support

². I hasten to point out that denial of access to insurance is not the only area of potential discrimination against those who do not fare well in the genetic lottery. For example, there are issues of social stigma, immigration policies, etc.

by governments. Obviously, much work has to be done. What the genome initiative will do is to make absolutely clear -- if we are not convinced already -- that we have basic concepts and values on a collision course. We can no longer postpone resolution of this troubling problem. I do not believe that insurance companies are necessarily the bad guys. But I do think that we need to go back to the drawing boards to explore ways of providing medical, life, disability and health protection for individuals. If we allow insurance companies to have access to information from genetic testing and screening, it is likely that we will undermine a push for resolution of the conflict. One of the major players will have little or no incentive to seek a solution. The push for change will thus rest on the shoulders of those least able to meet the challenge because of their existing vulnerabilities. My point is that we should utilize mechanisms that force rather than help us avoid such questions.

Another area of concern frequently raised by the genome initiative is the role of autonomy and choice in the provision of genetic testing and screening. The ethics of testing and screening have received much attention. The issues have been thoroughly considered, for example, by the National Academy of Sciences and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Moreover, there is consensus that mandatory screening, particularly in the absence of an adequate therapeutic intervention, is not warranted. Genetic testing to date has been

primarily for reproductive purposes. The future holds the promise of increased use of predictive medicine to identify susceptibilities -- susceptibilities that may not be realized for long periods of time and for which there will be no adequate medical intervention. Surely the conclusion that mandatory screening is generally not warranted is especially pertinent in the context of more powerful methods of testing and screening.

In my view, one remaining significant ethical issue needs exploration. This issue is pertinent to the issue of whether an individual has a right not to know genetic information. The provision of genetic services is characterized by permitting individuals to make appropriate choices for themselves. Yet, the provision of such services makes clear that in a real sense the patient is really the family and not the individual. The genome initiative is expected to facilitate our ability to offer such services and to make even clearer that the family rather than merely the individual is being treated. The work of Professor Nancy Wexler and others gives early clues that working with the family rather than just the individual poses new and different ethical dilemmas.

This is not surprising. There is general agreement that law lacks an adequate theoretical basis for understanding the institutional arrangements that define the family and the principles of moral decisionmaking that should guide the formation, existence or termination of family arrangements. Moreover, this deficiency is not confined to law. Political

theory and ethics have so far had relatively little to say about the family. As a result ethical issues that impinge on family arrangements have been inadequately conceptualized.

There are two primary frameworks for analyzing issues inherent in intrafamily decisionmaking. One approach frames the problem as one of sensible accommodation between rights-based liberalism on the one hand and communitarianism on the other. Yet, family matters do not fit comfortably into the framework. Family decisionmaking is not merely individualistic. Approaches that emphasize noninterference and individual preferences seem inappropriate and somehow "selfish." Moreover, resort to rights language has tended to put the individual's interests in opposition to the interest of others -- a result not necessarily desirable within the context of family. An emphasis on communitarian ideals, especially in their "strong" form, also seems misguided so long as we are unwilling to have substantial state intervention into matters that have heretofore been considered of a personal and private nature. Moreover, family relationships seem to require sustained and intimate attention to a degree that exceeds mere obligatory responsiveness.

A second framework conceptualizes the problem as a search for appropriate principles by which to resolve conflicts among family members. This approach assumes that appeal to generalizable principles is necessary in order to achieve coherence, consistency and impartiality in family decisionmaking. It also assumes that general principles can be successfully

applied in specific contexts. Yet, an appeal to principle seems inappropriate in the context of a relationship with particular others. In a relational context, the goal is not to have winners or losers but rather to choose among competing claims that are generated by significant connections to particular others. Individuals seek to accommodate their own preferences to the needs of particular others so as to maintain significant and mutually respectful relationships -- something that individuals are often unwilling to do in their relationships with "universal" others. Moreover, there is some doubt about whether resort to general abstract principles is of value at all in a relational context. The deductive and generalizable reasoning that their use requires may be too artificial and reductionist to take sufficient account of a specific context or the richness and complexity of relationships with particular others. Both frameworks are inadequate in a family context but they both could be usefully explored to understand the individual's wish not to know as weighed against obligation to family members.

While we have done a great deal to clarify the ethical issues in genetic testing and screening, we have not done the empirical work that is needed in order to prepare medicine and practitioners for the information that hopefully will flow from the genome initiative. We do not have a good idea of what currently goes on in the provision of genetic services. Some of this work has been begun by John Fletcher and Dorothy Wertz. Their early work, concerning sex selection in particular, reveals

interesting information that calls into question the strong reliance in all instances on patient self-determination and non-directive counseling. We need to know more about who has access to such services and the adequacy of services when provided. We need to know if some groups or persons are being seriously disadvantaged because there are barriers to access or barriers to understanding the terms on which services are being provided. This type of empirical work is expensive but it is important to do if we are in fact to prevent or reduce the incidence of misuse of genetic information. Policy makers and indeed those who are involved in the provision of genetic services as providers or recipients need such information.

In attempting to achieve some resolution of issues posed by the provision of genetic services, we need to spend more time trying to understand the public's values concerning these matters. This in turn leads to trying to assess the extent of public knowledge about genetics and the provision of genetic services. In my view, we have not made extensive enough use of techniques such as focus groups and polling that have been heavily used in political campaign decisions. These techniques are expensive but they have the promise of really providing public input into decisionmaking. Methods used extensively in the past are effective in getting the already interested member of the public to provide information, but they overlook members of the public who have views on subjects but are not motivated to express those views in specially created forums.

In conclusion we have a lot of work to do in creatively translating ethical concerns into public policy. We need to continue conceptual approaches to clarifying issues. But in the context of genetic testing and screening, it is imperative that we spend some time learning from precedents. We must be especially creative in getting the public involved in a consensus about these matters. That requires understanding the public's concern, appreciating the limits of public understanding and developing programs to educate the public about genetics.

The rapidity of scientific discovery has often outstripped society's ability to provide standards by which to evaluate these discoveries. Moreover, it has often outstripped society's ability to minimize the adverse consequences of discovery. The genome project offers the opportunity for the first time to anticipate and prepare for the consequences that scientific advancements will bring.

I will be pleased to answer any questions that you might have.

Senator GORE. Okay. Very good.

Dr. Olson, welcome again, and please proceed.

**STATEMENT OF MAYNARD OLSON, PROFESSOR OF GENETICS,
WASHINGTON UNIVERSITY SCHOOL OF MEDICINE**

Dr. OLSON. Thank you. My perspective like Francis' is that of a working scientist involved in this project. I would like to comment briefly on really three issues.

I was asked to say a few words about the technical state of the art—that is, is this project feasible, comment a little on my perspective on the potential benefits and then I want to mention a couple of policy issues which have already been raised, I will say a brief word about.

Technically, I think that there is every reason for optimism, that the project is feasible. I say that, however, only with the explicit follow-up that I believe that it is not true, as even many scientists regard it, as a matter that simply requires a scaling-up existing routine methodology.

Dr. Watson already alluded to this in his speculation that we must lower the cost of sequencing DNA by a factor of 10. That is one illustration of the fact that this is a project in which the technology is going to have to evolve rapidly as it is being applied.

And in that sense, it is a challenge to the infrastructure of American basic research to do something which industry is also being severely challenged to do. And that is to reduce new technology to practice on a large scale with a short lead time in the presence of a lot of underlying flux in how things are done.

I would just like to illustrate that slightly more specifically with respect to the physical mapping problem, which is one of my specialties, there was a new experimental method known as the polymerase chain reaction, the PCR as it is commonly called, which was first described in 1985 in a paper that many of us largely ignored.

There was a substantial improvement in the method published in 1988, which led to its widespread adoption. And it played a key role, for example, in Dr. Collins' cystic fibrosis work.

Now, the existence of this new method of recognizing landmarks along DNA has led to a proposal which I think there is an emerging consensus about to use as the basic landmarks in the forthcoming mapping, a class of sites known as sequenced-tagged sites, which can be recognized by the PCR.

The tremendous advantage of this mode of identifying landmarks along the DNA is that the landmarks can be completely described in a database.

Previous methods of identifying landmarks along DNA required both a database and supplementary biological resources, which are expensive to maintain, distribute and so forth.

My main point, however, is that we are looking at something which basically dates to last year, which is having a major effect on our thinking about the technical problem. And we are going to see this happening over and over again, as a rapid flux in the underlying technology.

With respect to the benefits of the project, we have heard a lot said about the substantive benefits to medicine, agriculture and so forth.

I would like to emphasize another side of this issue, and that is the extent to which this is a critical project for developing human resources within the American scientific establishment.

I think that it is now clear, as many witnesses have said, that the efficient analysis of genetic material has become critical technology from all areas of biology ranging from health-related research to bio-technology and agricultural science.

I think that even many biological scientists in their euphoria over the early successes of the recombinant DNA era fail to recognize the extent to which biology and medicine, bio-technology, are going to be revolutionized in the coming years by the simple ability to acquire DNA sequenced data efficiently and to analyze it.

It is a fundamental principle in science with respect to human resource development that path-breaking science attracts path-breaking scientists.

I think that the United States can ill afford to sit out this project, indeed, not to move rather aggressively on it, or else this reservoir of expertise will develop elsewhere.

The basic activities that we are talking about describing the human genome at the level of mapping and their level of sequencing, are activities that are going to be new only once in human history. And it is seizing that opportunity that will assure the participation of our best scientists in this effort.

And I personally think that that will probably be the major benefit for the United States in terms of our national interest, and I will come back to that just in a moment.

With respect to policy issues, Dr. Watson already mentioned the point that in some quarters the human genome project is being blamed for what in fact is a much broader crisis in the funding of basic bio-medical research in the United States.

And I think that is an issue that Congress will hear more about and bears watching. I believe that the contention that this project is a significant cause of the tight funding in basic biology now, is an illusion that would not withstand careful analysis.

I think the real cause has been explosive growth in the enterprise of basic molecular biological research. And this growth is indeed a response to the creation of the many research opportunities that Dr. Watson discussed.

Nonetheless, I think it goes without saying that it would be a mistake to divert funds to the human genome initiative at the expense of the continuing health of basic bio-medical research. And I think we all understand that.

If I may, I would like to close by just taking a slightly closer look at this issue, which has been discussed at some length already. And that is, where does this delicate balance lie between international competition and collaboration on this project?

I think that the key point here is to define the American national interest in this project rather carefully. And I think that where that national interest lies—that is, the specific national interest in addition to the general good that will come out of this project, is in the development of this world-class human resource that is having

first rate expertise in an area that will be coming steadily more important in modern genetics.

I think on this issue of availability of data, I mean, I certainly agree with Dr. Watson that there will be a lot more discussion about it. And I would come down and answer to your more specific questions more on the one-year category than, for example, three years.

It would be a catastrophe, in my opinion, to create secrecy within this enterprise. Francis Collins was unable to even maintain the normal prepublication embargo over the very exciting news from their laboratory. And I think that this is unavoidable, as was pointed out in a science editorial.

Too many people are involved. We are not going to have one person sitting at a computer terminal seeing the key biological information or the bio-technologically important information in a DNA sequence. At best, this person is going to have an idea, which then needs to be tested in many laboratories; complex collaborations will have to be set up.

And it will simply not be practical to embargo these data for what would, I believe, typically be several years before one could even take a serious first pass at seeing what was important in them.

So, my only real point here is that I think we would be misleading this committee if we told them that what they were buying and paying for the human genome initiative was some kind of proprietary American database that we would have a really substantial first crack at to skim the commercially important cream off of or, indeed, the basic scientific discoveries.

I think that the American interest lies and will be adequately served in this area of human resource development.

Thank you.

[The statement follows:]

From: Maynard Olson
 Department of Genetics, Box 8031
 Washington University School of Medicine
 St. Louis, MO 63110

Re: Testimony before the Senate Subcommittee on Science, Technology, and
 Space: hearings on the human genome initiative, November 9, 1989.

To place my testimony in context, I should identify myself as an active researcher with a special interest in the technical problems associated with the analysis of the human genome. I have also been involved for several years in the advisory process from which current policies towards the human genome initiative have emerged. From this perspective, I would like to comment briefly on three key issues: the technical state of the art, the potential benefits of the project, and the need to address certain outstanding policy issues.

Technically, there is every reason for optimism that a well managed project will be successful. However, this optimism should not be mistaken--as it often is by scientists and non-scientists alike--for the view that the initiative will simply require the routine application of existing experimental techniques on a large scale. It is my judgment that the successful experimental strategies will bear little resemblance to the way that most DNA mapping and sequencing is now carried out. If correct, this view implies that we must carry out pilot studies on candidate mapping and sequencing strategies at the same time that we are scaling up our overall capacity for genome analysis. Success in this venture will require tough management. Funding of genome-analysis projects will have to be sufficiently stable that strong institutions and strong individual researchers are willing to commit themselves to the venture, but not so stable that projects that are unable to meet the technical and organizational challenges cannot be terminated. In many respects, this project requires the infrastructure of American basic research to meet a challenge that also faces American industry: to reduce new technology to practice on a large scale with a short lead time.

With respect to the soundness of the underlying technology, I would like to start with physical mapping. There is a consensus that the first phase of the project should concentrate on the development of a reliable physical map of the human genome. Such a map would do for the human genome what conventional topographic maps do for the surface of the earth: provide a precise description of the spatial relationship between easily recognized landmarks. As in conventional cartography, the nature of the primary landmarks is unimportant as long as they are easily recognized (e.g. one starts by mapping mountains, rivers, and coastlines; at a later stage, one maps population density, voting patterns, etc.).

With respect to landmarks, the good news is that a powerful new experimental method--the polymerase chain reaction (PCR)--allows short tracts of human DNA sequence to provide easily recognized landmarks. As an illustration of the pace of technical developments, the PCR was first described in 1985 (1). A major improvement, which led to its widespread use, was published in 1988 (2). Now, there is an emerging consensus that the adoption of PCR-based landmarks called Sequence-Tagged Sites (STSs) would solve two major problems in the human genome project (3,4). First, enough information to allow recognition of an STS can be described in a simple data base, whereas

previous landmarks could only be recognized with the aid of biological reagents--usually recombinant-DNA molecules--whose cataloging, archiving, and distribution are slow, expensive, and unreliable. Secondly, by providing a "common language" for physical mapping, STSs allow mapping results from one laboratory, obtained by any method, to be checked quickly in another laboratory using a different method. This capability is essential for the management of the physical mapping: it introduces an element of quality control that is essential if individual projects are to be kept accountable.

A second area of progress has been in the ability to construct and propagate recombinant-DNA molecules that are much larger than those employed during the first decade of recombinant-DNA research. The best characterized example--the "YAC" system--employs yeast as the host cells. Not only does the use of large molecules reduce the number of steps required for the segmental analysis of the human genome, but there are encouraging indications that the yeast system may allow a significantly higher fraction of the genome to be recovered in recombinant-DNA molecules than was possible with previous methods. As another indication of the dependence of the human genome initiative on rapidly emerging technology, the YAC system was first described in 1987 (5), and the first publication of its use to recover a specific, well characterized segment of the human genome appeared only last June (6).

My technical judgment is that the physical mapping of the human genome is likely to proceed most efficiently by an adroit combination of PCR and YAC applications. Other experts, of course, have their own opinions. For this Committee, the relevant point--on which I believe there would be little technical disagreement--is that the development of a map over the next several years will require a challenging combination of applying technology that is qualitatively new to an objective that is quantitatively imposing.

With respect to DNA sequencing--the actual determination of the "code of life"--the situation is somewhat different. Current large-scale sequencing projects primarily employ technology that has undergone only incremental changes during the last decade. However, the impact of major new instrumentation, which eliminates some of the manual steps in DNA sequencing, is beginning to be felt. The first publications on these new instruments appeared 1986-1987 (7,8). The combined effects of new instrumentation and incremental improvements in the underlying technology, appear to have brought the sequencing of the human genome within reach. However, few scientists would advocate initiating more than pilot-scale projects without pursuing further refinements of sequencing technology. The most rational objectives for pilot projects are carefully chosen regions of the human genome and the entire genomes of selected simpler organisms. The most attractive candidates for these model organisms are species such as *E. coli*, yeast, and the nematode worm *Caenorhabditis elegans*, all of which play central roles in basic studies of genetic function. Improvements of a fewfold in sequencing efficiency, which should be achievable without unforeseen breakthroughs, would bring the cost of sequencing the human genome into the \$1-2 billion range. Even given adequate funding, it is likely that the rate at which the project could proceed would be limited by the number of scientists with the necessary combination of technical and managerial skills.

With respect to the benefits of this project, I would like to emphasize the importance of the human resources that will be developed if the United States carries out a well managed human genome initiative at a funding level comparable to the \$200 million/year recommended by the National Research

Council Committee on Mapping and Sequencing the Human Genome (9). The efficient analysis of genetic material has become critical technology for all areas of biology, ranging from health-related research to biotechnology and agricultural science. I believe that even many biological scientists, in their euphoria over the early successes of the recombinant-DNA era, fail to recognize the extent to which biology will be transformed over the next decades by continuing, open-ended advances in our ability to acquire and analyze DNA-sequence data. If the United States is to lead in these areas, building on its impressive existing strengths in the biological sciences, it is essential that we develop a generation of scientists with unsurpassed abilities in this area. The only way to attract and develop the needed talent is for the United States to take the initiative in the analysis of the human genome. Pathbreaking science attracts pathbreaking scientists. There is, at present, a historical opportunity for the United States to lead in an activity that will be new only once: taking our knowledge of the human genome from its present primordial stage to a level of detail that will become a basic tool for all future biology. In the process of developing this project, we will insure that the United States enters the twenty-first century with world class expertise in a technology that will be even more important upon the completion of the project's initial goals than it is now. The expertise will undoubtedly be distributed throughout the American scientific establishment: in the universities, in the national laboratories, in the biotechnology industry, and in entrepreneurial ventures that arise to provide specialized products and services for the project itself.

I would like to close by addressing two policy issues that require close monitoring. The first of these concerns the internal structure of basic biological research in the United States. There is a significant crisis developing in the funding of biological research, particularly with respect to projects designed to advance our understanding of the most basic processes that occur within cells and organisms. The symptom of this crisis that is most visible to a working scientist is the fraction of highly meritorious grant applications to the National Institutes of Health that are actually being funded. Trends in this area are alarming. Full exploration of this problem is beyond the scope of the present hearing. However, the problem is relevant to the human genome initiative in that even current expenditures on this initiative are widely seen both by grant administrators at the NIH and within the scientific community as a major cause of tight funding in other areas of biology. Even a cursory examination of the raw budget figures shows that the real problem lies elsewhere: in response to spectacular progress in molecular genetics and cell biology, there has been unprecedented recent growth in the number of laboratories, the size of laboratories, and the cost of increasingly high-technology experimentation, throughout the basic biomedical sciences. This growth is outstripping the growth of the relevant NIH budgets. The problem bears close monitoring by the NIH, other agencies, and the Congress since funding policies in this area will profoundly affect the future health of biomedical science in the United States. It goes without saying that basic research in biology is the "goose that laid the golden egg" with respect to the present opportunity to mount an effective genome project. Funding of the human genome initiative must not come at the expense of sustaining the health of the basic biological sciences. On the other hand, our ability to take new initiatives when historical opportunities arise cannot be held hostage to the implementation of an ideal solution to the much broader problem of funding explosive growth in all areas of basic biology.

The final policy issue that I would like to address concerns the delicate

balance between international competition and collaboration in human genetics. Since there is nothing that more fundamentally unites all humans than their membership in the same species, the human genome is a natural area for international scientific collaboration. Many multinational collaborative projects are presently underway, and such efforts should be encouraged. Nonetheless, the United States should not make its activities in this area contingent on the negotiation of international agreements. The principle that should guide American policy is that this project is strongly in the national interest for the reasons discussed above: it offers an unparalleled opportunity to develop world class strength in an area of technology that will be increasingly critical in the coming decades. If the United States takes the lead and generates much of the basic data about the structure of the human genome, many other countries--including our major economic competitors--will inevitably benefit from access to the data. It is neither desirable, in principle, nor feasible, in practice, to restrict access to these data. The competitive advantage that we will gain by investing in this project will be enormous nonetheless. Energy should not be diverted to futile and divisive discussions about access to research materials and data. The real challenge before us is to develop a strong program that is broadly integrated into the American scientific establishment. If we succeed in this objective, there need be no concern that the specific American national interest is being well served.

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Senator GORE. Thank you. Dr. Wexler, we are going to have to briefly recess for the vote on the floor, and we will come back and get your testimony. And then we will have questions for the full panel.

I anticipate the recess will last about 10 to 12 minutes.

[Recess.]

Senator GORE. The subcommittee will come back to order.

Dr. Wexler, we were about to hear your testimony. Please, proceed.

STATEMENT OF NANCY S. WEXLER, ASSOCIATE PROFESSOR,
COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY

Dr. WEXLER. Thank you very much.

It is really a pleasure to be here. And I am sure this is out of order, but I would like to ask you to join our committee as an honorary member of the ethics working group, because I do not think I have heard anybody lay out the issues really as cogently and as articulately as you have here today.

Senator GORE. You are off to a good start, Dr. Wexler.

Dr. WEXLER. So are you.

Senator GORE. Thank you.

Dr. WEXLER. I think you have a very good sense of what we are up against. And I think all of us take very seriously the mandate to try to anticipate these problems before they occur and to try to act peremptorily as you said.

There is a tremendous amount of benefit to be gained, and we would like to maximize the availability of that benefit and minimize any potential hazards.

Briefly, the program that the ethics working committee has outlined, of which Pat King is a member, is a kind of tripartite program. One would be to stimulate research in the community. And these are researchers that do not usually get NIH grants, they are ethicists, they are lawyers, they are humanists.

Also, to have our own research agenda refined, through interdisciplinary workshops and position papers. We would like to stimulate much broader public discussion through public testimony and hearings, and we would like to develop policy options and possible legislation, perhaps in concert with this committee or other committees that have relevant interests.

We feel that the scope is very, very large, and we do include, although it is called the ethics working committee, there are specifically legal and social issues that are relevant. I would like to focus on one of these issues in this testimony, because I think it is really an overarching concern, and it stems from the way that the science is done.

The long-range goal of the Human Genome Initiative is treatment, prevention and cure. But the initial benefits of the science are going to be in detection. And for a while we are going to be in an interim phase in which you can detect, but you cannot—yes, I agree with that sentiment totally, and I think that really is a major problem.

With certain diseases, detection will be an immediate benefit. If you know that you are that percent that has X number of genes for lung cancer, you can target every single smoke enders program to that person. If you know you have atherosclerosis, you can really make lifestyle changes.

But there are other diseases, for example, Huntington's disease, for which you can now test somebody and really, with almost 100 percent accuracy, tell them if they will die in the future of this neurodegenerative disease, and there is nothing that you can do to prevent or treat it.

If there was Alzheimer's disease, it will be that category of test, and I think that that is likely in the future.

So, there will be some diseases for which we can have treatments, and others, for which, for some interim period of time, there will be nothing. And it really is in this interim phase that we have the most concerns. There is the problem of insurability. There is the problem of stigmatization and labelling.

Let me just give one brief example here, and I think it goes along with what Francis Collins was saying about cystic fibrosis. If one in 25 of us is a carrier for cystic fibrosis, that means there are many of us in this room who are carriers for cystic fibrosis who suddenly learn this. And I think if you suddenly think about yourself as a CF carrier, you begin to think a little differently, and you begin to wonder what your partner, or what your boyfriend or girlfriend is. Psychologically it has an impact.

Now, we do not know how the insurance companies are going to respond to this. You are perfectly healthy, but are your premiums going to change depending on who you are dating?

I think that these are questions that we have only just begun to really think through. We do not know when to provide the test. Should it be at birth? Should it be when you get a marriage license? Should it be as part of routine genetic services? In which case you may have fewer reproductive options open to you.

So all of these are issues with which we have to deal.

Now, I think the major commitment, ethically, legally and socially, we need to make in starting this project is to see it through. Because it is in the final stages that we will really see the fruits of this labor. If we end in this halfway zone, then I think we are in deep trouble.

And this brings us to another problem of the funding budgets.

Now, I would like to help Dr. Watson from being attacked by his scientific peers, but I think that there really is a major reason, ethically and socially, why these budgets at the NIH and at ADAMHA must remain high. The Human Genome Initiative is there to make the general map, cities, towns, light bulbs, to work out when the light goes out how to fix the filament. That is the job of the NIH.

The genome initiative does not have that money. So now the problem is, if Francis finds the CF gene, who pays for the cure? If he then goes to the NIH and they cannot fund that research, all of those little kids out there are going to have the benefit of knowing the gene is isolated, but there will not be a better treatment.

And I think that really could be a potentially disastrous situation, to sit in hiatus between detection and cure, with no research funds to do the work.

And I would just like to say that I share the sentiment of sins of omission and commission. I think that we are in a stage now that we have a commitment to people to do something when we have the capacity to do it, and we need to press on with it.

Thank you.

[The statement follows:]

Nancy S. Wexler, Ph.D.
Associate Professor
Clinical Neuropsychology
College of Physicians and Surgeons
Columbia University

The plan to map and sequence the human genome has profound implications for the alleviation of human suffering due to genetic disease. Genes directly causing or predisposing to human disease will be placed on the map for all to investigate. Additionally, normal genes which may be involved in pathways leading to the development of new treatments will be captured and fundamental biological lessons in genetic regulation and functioning will be learned through the Human Genome Initiative.

Any scientific endeavor of this magnitude must be developed in concert with a plan to ensure that the public has access to benefits in improved health care which should be a result of the research. It is also imperative to protect individuals and society from possible hazards which may be a consequence of our improved ability to detect and predict hereditary illness. The use of genetic information, for good or ill, has long been an issue in our society. But the quantity and complexity of genetic information which should become available requires that special precautions be taken.

Accordingly, the National Center for Human Genome Research is giving high priority to the development of a program to address the ethical, legal, and social implications of the Human Genome Initiative. This plan will attempt to anticipate the impact of the Human Genome Initiative and address what protections need to be in place so that the information generated can be of maximum benefit to individuals and society.

In order to be maximally responsive, the Program Advisory Committee on the Human Genome established a working group on ethics to develop a plan for this component of the Human Genome Program. Its purposes will be to:

- 1.) anticipate and address the ethical, legal and social consequences for individuals and society of mapping and sequencing the human genome, particularly before problems may arise.
- 2.) stimulate public discussion of the issues.
- 3.) develop policy options that would assure that the information is used for the benefit of individuals and society.

One request for grant applications in these areas has already been issued and another is now pending.

The working group is currently developing its agenda but it has identified the following issues to be of particular concern; here research is encouraged and possible policy development or legislation may be needed.

EQUITY IN THE USE OF GENETIC INFORMATION

Genetic information must be used fairly. It must not be used as the basis on which to discriminate or deprive an individual of rights, access or property.

This concept particularly applies to the acquisition and maintenance of insurance of all types. The insurance companies are currently unresolved as to the impact of a range of possible future tests for genetic diseases or predispositions. As increasingly large numbers of people are found to have these conditions, there may be a danger that they will become uninsurable or have to pay exorbitant premiums. If an insurance company pays for prenatal testing, does it then have a right to influence a couple's choice regarding the outcome of that pregnancy by refusing to pay for the medical care of a child born with a genetic affliction? Or must the company pay both for testing and care? The insurance companies are grappling with these issues.

There is a danger that genetic tests may be used to preclude some from employment, from certain types of education or training, or from entry into the military. If a chief executive officer of a large corporation is prone to develop manic depression, or an airline pilot is destined to have a fatal heart attack or a stock broker fated for Alzheimer's disease, is it in the best interests of the public to preclude these individuals from positions in which they may do harm or others? Or is it best to focus on "functionality," rather than "potentiality," and emphasize increased medical surveillance and care, perhaps provided through the workplace? Existing protective legislation is being reviewed and some additional laws may be needed.

PRIVACY AND CONFIDENTIALITY

The privacy and confidentiality of genetic information is paramount and additional protections may also be needed in these areas. If an insurance company pays for a genetic test, does it then have the right to know resulting diagnostic information? Should all tests be totally voluntary and subject to informed consent, or should some be mandatory, as are some newborn screening tests for certain genetic conditions? There are precedents for both types of testing and significant variation from State to State.

The wealth of new genetic knowledge can have a profound effect on individuals and their position in society. More subtle forms of discrimination can intrude such as stigmatization, ostracism, and loss of personal self esteem through genetic labelling. On the other hand, as there is almost no one that some genetic vulnerability does not touch, we may find a heightened sensitivity and tolerance.

GENETIC PROPHECY

The practice of medicine will be profoundly altered by the availability of new tests for genetic diseases and dispositions. In many instances, improved early warning systems of vulnerabilities to certain types of cancer, heart disease, hypertension or diabetes can lead to appropriate alterations in life style, diet or the frequency of medical checkups.

In other instances, however, prognostications about future disability can be given to people who are currently healthy but destined for irrevocable decline. There is a new test available which can tell people at 50% risk for Huntington's disease, a fatal neurodegenerative disorder usually of midlife, if they are carrying the lethal gene. This test suddenly thrusts the stark question before us of whether we wish to know how and when we shall die of a disease, if there is nothing medical to be done.

FUNDING FOR GENETIC DISEASE RESEARCH

The key solace for people receiving bad news from the Huntington's disease and other similar tests which will be developed in the future is that "science will find an answer" in time for them. But this consolation brings up another potentially grave problem: will the funds be available through the National Institutes of Health and the Alcohol, Drug Abuse and Mental Health Administration, whose mandates include categorical disease research? If the funds are cut from these institutes, just when they most need monies to take advantage of the new knowledge being unearthed by the Human Genome Initiative, we could be left in the untenable situation of being able to prophesy disease but not to prevent or treat it.

The true promise of the Human Genome Initiative lies not in detection but in treatment. The capacity for developing genetic tests for diseases will come first because it is a necessary first step along the path of finding a gene, discovering its defect, and developing a cure. But prediction is a way-station; therapeutics is the goal.

It is difficult to know what knowledge may need to be in place to eradicate even one disease. Finding an abnormal gene on one chromosome may not suffice. If the mutant gene itself is too intractable, perhaps manipulating genes in pathways it controls or experimenting with modifying genes will be a solution. Funds for the Human Genome Program and categorical disease research support must not be at the expense of each other.

IMPACT ON GENETIC SERVICES AND MAINSTREAM MEDICINE

There are numerous questions which will arise as additional disease genes are identified which need to be addressed in a thoughtful way. For example, one in 25 Caucasians carries the gene for the fatal recessive disorder of children and young adults, cystic fibrosis. One in 625 unions will be between two healthy carriers. Their children have a 25% chance of inheriting both cystic fibrosis genes and developing the disease. The gene causing this disorder was recently isolated by Drs. Francis Collins, Lap-Chee Tsui, and John Riordan, making population screening now possible. This is an extraordinary opportunity, but it poses taxing questions. When should people know if they are carriers? At birth? In school? Prior to getting married? Prior to having children or after they have conceived? Each possibility has different social, psychological, financial and medical costs and benefits.

There have been concerns voiced that, as additional tests are developed, people will be pressured into having the so-called "perfect baby." Aside from the fact that there is no such thing, a key tenet of genetic counseling is individuals' freedom to avail themselves of information only as they choose.

Introduction into mainstream medicine of our increasing genetic information and the options for improved medical care which will follow is a challenge. There must be heightened attention to the qualifications and continuing medical education of medical and allied health personnel. The specialty of genetic counseling must be responsive to the wealth of new data and the numbers of potential clientele wanting to know its relevance for them. There are now more reproductive options open for an ever growing number of conditions. It would be a tragedy if advances in genetic information are ushered into medical practice through malpractice and wrongful life suits.

PROPERTY AND PHILOSOPHY

There are questions raised by the commercialization of products from the Human Genome Initiative which require our attention, even as some are being decided by the courts. The Human Genome Program will undoubtedly generate numerous patents, copyrights and trade secrets. We do not yet know what impact this may have on the scientific collaboration and candor which is required for such a massive undertaking. With so many working so closely together, how will issues of priority and proprietary rights be resolved?

In addition to its profound medical impact, the Human Genome Initiative raises conceptual and philosophical issues. As the genetic underpinnings of health and behavior are being unraveled,

what will be the role of free will and human responsibility, and how does the environment contribute?

There are some who paint dire scenarios. They point to the eugenics movement which once flourished in the United States and the atrocities committed during World War II and warn us that mankind is capable of distorting genetic information in the service of harm and prejudice. This is not the fault of genetics but of our capacity, genetic or otherwise, to hurt our fellow human being. Open, free discussions and a vigilant eye are needed to guard against the misuse of these and any other medical or social data which can be misconstrued.

PROGRESSING INTO THE FUTURE

There are sins of commission and sins of omission. We must ask ourselves "what are the ethical consequences of not proceeding when we are able?" Once we have the capacity to move ahead, if we choose not to we are consigning some people to certain death as surely as if we were withholding antibiotics or oxygen. We no longer have the excuse that there is nothing to be done. But if we proceed, in a thoughtful, careful and responsible manner, we have the potential for bringing freedom from suffering, pain, and fear in ways not yet imagined. The magnitude of the challenge is dwarfed by the magnitude of the possibilities.

Senator GORE. Well, thank you.

And let me thank all members of this panel. We will go to some questions now, but your opening statements have been very, very helpful.

Dr. Olson, 18 months ago you testified over on the House side, and I quote, "It is a bit of a scandal that we do not know what the accuracy of the DNA sequence is. The fact of the matter is that not one cent has been spent estimating what the error rate is, even in this existing set of data."

Has this situation improved? Has the independent quality control mechanism, strongly recommended in the NRC report, been put in place? Or is this less of an issue due to advances in technology?

Dr. OLSON. I think that it is slightly less of an issue. The accuracy of DNA sequencing has certainly gotten better for various technical reasons. I think it is still a bit of a scandal.

I was at a meeting in Virginia two or three weeks ago in which the world sequencers assembled and had a panel discussion on sequencing accuracy. And I do not know how my colleagues who were there reacted, but I found the discussion totally unedifying. They were unable even to define accuracy, much less to suggest any test for it.

I think that that problem needs attention.

Senator GORE. Does anybody else want to comment on that?

[No response.]

Senator GORE. No? All right.

Doctor Watson, Doctor Wood, if you find yourselves anxious to comment on something, you are most welcome to come back up to the table.

Dr. Collins.

Dr. COLLINS. Perhaps one of the excuses for not pushing this so hard may relate to the fact that current sequencing technology is

not what is going to be applied to the large-scale effort. If we determine to the second decimal place what the error rate is with our current methods, that may not be the right answer for the methods which are actually used.

I think some people have said therefore, let us wait until we really know what we are going to be doing. I am not saying that is the right answer, but it is, in fact, a reason that has been given.

Senator GORE. All right.

Let me shift gears. I referred earlier to the hearings that I conducted on the House side. In 1984, I requested a study by the Office of Technology Assessment on human gene therapy. During that study, they concluded that germ line therapy raises very, very serious ethical questions.

It is so unlikely that we will be able to master that ability that we can afford not to get too worked up over it.

Do you believe, Dr. Collins, that sequencing the human genome will improve our ability to do gene therapy, both somatic and germ line?

Dr. COLLINS. That is a good question.

The distinction, of course, between somatic cell gene therapy and germ line gene therapy is a crucial one. In somatic cell gene therapy you are replacing or inserting a gene into a particular organ or tissue to try to compensate for some defective gene. You are not doing something which will then be passed on to future generations.

With germ line therapy, however, whatever you are doing is getting into the germ line and will run the risk of creating havoc in future generations that you might not have anticipated. This is the major concern about this approach, that maybe we will never be smart enough to really know the long-term effects.

What you have just said, namely that germ line therapy in humans is not an appropriate step to take right now, is still very much true.

The genome project, by its provision of a large amount of data, and the identification of genes which cause disease, will undoubtedly lead to an increase in the potential for somatic cell gene therapy.

CF is a good example. We are already initiating an effort to develop a somatic cell gene therapy approach for this terrible disease. Such an approach was absolutely impossible until the gene was in hand, but now it is.

This will be true for other disorders as well, with varying degrees of difficulty and appropriateness.

It is perhaps correct to say that identifying more genes may increase the potential for doing inappropriate things in the way of germ line therapy.

If you try to think, however, of specific instances where a germ line approach would be the only way you could correct a particular disorder, it is difficult to think of such examples.

Senator GORE. Does anybody else want to comment on that?

Dr. OLSON. I would just agree that the prospects are still remote. It does not mean that they are non-existent, but they are remote, for purely technical reasons.

Senator GORE. So this gap between diagnosis and cure that you talked about, Dr. Wexler, is likely to be a persistent problem.

I have read, Dr. Wexler, that you have a particular interest in Huntington's disease, which you mentioned, and you may get tired of being asked this question, but I understand that one of your parents was stricken by it, and that you have a 50/50 chance of carrying the Huntington's gene. How have you dealt with that knowledge?

Dr. WEXLER. That is what makes me come here.

I think one of the things which is particularly true of genetic diseases is that they are family diseases. The entire family is involved over many generations. It was my grandfather, three uncles, my mother, cousins, and my sister and I have a 50 percent risk.

And you can see that there is a certain certainty of this disease appearing over and over again. The only answer for us was in the research and in seeing it through to some kind of treatment or intervention. And I think many families with genetic diseases feel that way.

I think it is important to put in the protections and the preventions. I would never say stop the research; I would say use all of your imagination to protect people as best you can, because when the treatments are here, these problems will be over.

When people take a test and they test positively, if I could give them a pill, there would be no problem with all of the depressions and anxieties, but we do not have the pill yet.

Senator GORE. So you chose not to take the test?

Dr. WEXLER. Well, I think that this is something which I still struggle with. And I think that there are issues of timing. People make decisions some days that they may change.

There are issues that come up in your life that require planning, there are issues of children, which can entirely change your thinking about the value of a test or not a test. But I think that what happened with the Huntington's test, in our own family and in many other families throughout the world—I mean we were quite adamant, all of us, that a test should be created. My own personal research was to help develop a test for Huntington's disease.

And when something is not available you want it desperately. Because all you can think about are the things that you cannot do because the test is not there. If it is there and it is under your own control, whether or not you use it, then I think you can really think about the fact that knowing—if I were to know right here today that I am carrying the Huntington's disease gene and I knock over this glass of water, which would be easy for me to do, and I know I have the gene, I am going to have to sit here and struggle with myself about, is this the first symptom, rather than spending my time and energies trying to figure out the ethical program for the Human Genome Initiative. And I think that is a more worthwhile expenditure of energy.

These are very personal decisions. The counseling requirement for these tests is enormous. It is not available. It is not paid through insurance. And I foresee that there are certain aspects of the Huntington's test which are precursors of other tests for other psychiatric and neurologic diseases.

Senator GORE. Some of them have been raised in the more conventional context with the AIDS test.

Dr. WEXLER. Exactly right.

Senator GORE. And we have seen how quickly that context has evolved and how the consensus only a year ago was that it was inadvisable for most people to be asked to take an AIDS test, and now the consensus has completely changed.

Dr. WEXLER. Because of AZT.

Senator GORE. Because of AZT. That is exactly right.

Dr. WEXLER. Well, people have to have hope. If you give somebody the test and they test positive, and you ask them if it is likely to develop Huntington's, many of them say no. They know that they have the gene, it is 100 percent, and you ask them why, and they say, God will find an answer or science will find an answer, which is maybe both the same thing.

So people need hope——

Senator GORE. No, Doctor, I am sorry. Not in my view.

Dr. WEXLER. I agree with you on that one, too.

Senator GORE. Go ahead.

Dr. WEXLER. I think that for some people it is that they are expecting to be rescued. So whatever you tell them, people have to have hope. I think that that is sustaining.

And I think that for many, many people who have genetic diseases in their family, the Human Genome Initiative is the most hopeful and exciting prospect in all of their lives. And it is just rejuvenating everyone.

Senator GORE. If it becomes possible some day, as a result of this work, for everyone to know what their own personal genetic map is, that knowledge could transform our attitudes about ourselves and others. The phrase to know yourself would of course have a whole new meaning. And one would be able to start resolving some of the old questions about nature versus nurture and determine the extent to which genes do indeed affect destiny.

Perhaps we will find that our genes have a greater role or a lesser role in shaping personality than presently thought. That could lead to a certain fatalism. But related questions are among those which I think ethicists and sociologists should begin looking at right now.

Do the four of you agree with the conclusion I reached earlier that DOE should devote a comparable percentage of its funding to the identification and study of these questions, as does NIH?

Dr. Collins.

Dr. COLLINS. I am not sure about the mechanism, whether it makes sense to have two separate ethical bodies.

Senator GORE. I agree with that.

Dr. COLLINS. As far as funding, however, I completely agree.

Senator GORE. Well, presumably the agreement now under discussion between NIH and DOE could avoid duplication of effort but arrive at a commitment by DOE to match the levels provided by NIH or the percentage.

Professor King, do you agree?

Ms. KING. I agree about the funding point. I think I would like to think a bit more about the duplication issue.

Between Energy and NIH, it makes sense not to have any duplication. They are government agencies, they are all executive branch.

But with value questions, unlike the basic science questions, I am not sure that replication does not have a unique value.

There are values that go into judging what is important and what is not important, and those values are only as good as the diversity of the people that are doing the judging. So I will not be so quick to say that some replication or some duplication would not be warranted.

I am not sure, however, that I would put it, duplicate it within the federal establishment.

Senator GORE. Yes. It could be NIH and the Georgetown Law Center, for example.

Ms. KING. Absolutely.

Senator GORE. Dr. Olson.

Dr. OLSON. Yes. Well, I certainly agree with you on that point.

I think the only comment I would make is I think it was sort of a pioneering step to establish this policy early on by Dr. Watson, and I think the only thing I would say about it is that I think we probably do not know yet what level of funding will be required to do what can productively be done in this area. It is an open-ended issue, and I do not think we want some fixed ratio. I would not be surprised if 3 percent turned out to be low.

Senator GORE. I think I know your views on this, Dr. Wexler.

Dr. WEXLER. Yes, I would certainly advise against it.

No. I think that we have actually begun conversations with the DOE, and specifically I think they have concerns about the problem of genetic screening in the work place.

They have some particularly focused concerns and we would like to be able to expand the working group to include members selected by the DOE.

I certainly think that making a financial commitment confirms their commitment to this entire area and its value and its necessity to be part of the genome initiative.

Senator GORE. All right. Very good.

Another part of the NIH program involves public education. Someone has already mentioned the eugenics movement of the 1920s and the developments that followed which so horrified humankind and still haunt humankind.

I think that history gives particular urgency to the public education component of the NIH program.

Do any of you have suggestions on how that part of the program ought to be pursued or structured?

Ms. KING. I may teach, but I am not an educator in this sense. But I have one initial thought, and it is something I said before and that is, before we begin to structure an educational effort I think it is very important to try to understand the public's conception, existing conception, of genetics, of genetic screening and counseling, of their views about tampering with something so basic as a human genome. Not for the purposes of defeating the project, but for purposes of understanding how to direct our educational efforts.

I am somewhat leery of having persons, like the people assembled on this panel, really make judgments about what people that

are not like us are concerned about. And these issues not only vary across class, they vary across racial and ethnic and, indeed, gender groupings as well.

If you were to go into a black community, I am convinced, and to ask people about their attitudes about doing some of this work, one would get very harsh expressions in some instances, expressions of great fear because it is in that community that we realize that some of these eugenic issues did not end in 1920.

Senator GORE. Right.

Ms. KING. That some of these efforts are of recent vintage. The sickle cell screening programs, for example.

And I think it is very important that before we launch out in terms of what we want to do in education that we simultaneously at least have some understanding of what the public understands about these issues to begin with.

And I think focus groups—I have spent more time recently with these kinds of efforts. And while I do not think they are perfect, I do think there is a logic behind identifying groups of people to have discussions with, identifying issues and the ability to learn something.

And so that would be what I would urge.

Dr. OLSON. My main comment on the educational issue is a narrow one but I think important. And that is that, I think it should not be entirely uncoupled from the science itself. That is certainly not the whole problem.

But when we talk about educating the public we tend to talk about engaging them in discussions about these rather high level and vexing ethical issues when, I am sure, that if you did a poll even of the educated public, say the college-educated public, that you would find that the ignorance of even the most basic facts of genetics was profound. It is taught extremely badly in high school biology courses and barely touched below that level.

We have this irony that we have 10-year old kids who can tell you the order of the planets out from the sun and recite the various types of eclipses, and they know nothing about genetics. It is as though the Copernican revolution was still the active issue in modern science.

I think that this may not be a job for the NIH; maybe the NSF should get involved. But I think it is an urgent need in the public school curriculum to develop genetics instruction.

Dr. WEXLER. I concur with both of those points. In fact, the ethics working group did meet with representatives from the NSF and the National Endowment of Humanities, and we will probably work together with them because they have a great deal of experience in, particularly the NSF, in educational issues.

The one addition I would make to Pat's remarks though is that I think that there are certain universalities across classes and races and cultures, and that is a feeling of parents for their children.

I work in Venezuela, and they are radically different in many ways and desperately poor. And their major question to us when we go down every year on a NIH supported-research project is: now, will there be anything for my children and grandchildren?

And I think that we need to be able to provide enough education so that people know how to ask at the medical services for certain

kinds of programs that will be available for them; certain kinds of tests that will exist; certain kinds of medication that would be more relevant for people with certain genetic predispositions.

So I think we have to work both at the community level, just to give them the basic vocabulary of what runs in my family, who causes it, can I find out about it, what are the basics of genetics, what are the basics of probability, so that they can interact with their mental and physical health facilities.

And at the same time we have to improve the introduction of this genetic information into mainstream medicine, because many, many doctors do not have a clue about genetics. They do not provide good counseling; they never refer to a genetic counselor—there is not one around. They give people wrong probabilities. They say for a recessive disease, lightning never strikes in the same place twice. So, of course, you know, the next child is born affected.

Some of this is improved a little bit because of malpractice suits and because of wrongful life suits. And I think that really is a catastrophe and it is exceptionally expensive and increases the insurance of the doctors so that they do not want to get involved either.

So I think that we really have to improve the way genetics is taught in the medical schools and continuing medical education, and somehow then get the doctors and the public together to provide good services for each other.

Senator GORE. I had a set of hearings a few years ago on alternative reproductive technologies and in connection with that, OTA did a study of the medical professions. And, indeed, as you just said, the level of knowledge about basic genetics can be surprisingly low.

I had a hearing a few years before that on Agent Orange, and the chief of medical services for the Veterans Administration testified that birth defects in the offspring of soldiers exposed to Agent Orange could not possibly be due to genetic damage done to the soldiers because, he said, such traits can only be passed on by the mother.

I noted at that time that thousands of years ago, primitive man thought that the mother was the only one who had anything to do with the birth and with the conception. And that view was subsequently proven to be wrong. I allowed as how I thought that his view would meet the same fate.

Ms. KING. Senator.

Senator GORE. Yes.

Ms. KING. I have noted the points of Dr. Olson and Dr. Wexler, and I do not disagree. But I want to underscore a separate point. And that is, it is not just that we have a lack of knowledge about genetics on the part of the public and on the part of practitioners. It seems to me that in the provision of genetic services, that is not the only issue.

A part of the other issue is the devastating impact that it has on people to learn that you have certain kinds of genetic disabilities. And the sensitivity with which that is handled in the clinical process across class and racial and ethnic groups is critical.

So a part of my point about learning about differences in views about genetics, its impact, is to go to help us all to learn better, not just the genetics part of this, but also how to implement programs

effectively so that we do not continue to perpetuate some of the problems that we have had in the past.

Senator GORE. Well, that is so important and I want to underscore that.

We heard earlier from Dr. Wexler that many with a family history of genetic diseases look to the human genome program for hope. Yet it may be that because of the program, we will become more proficient at diagnosing genetic diseases without becoming more proficient at treating them and so the program may take hope away, unless we match our commitment to this project with a comparable commitment of resources to counseling, prevention, treatment and the development of a body of knowledge to meet the need that you have just isolated and identified, Professor King.

You wanted to comment, Dr. Collins?

Dr. COLLINS. Yes. I think you can tell that you have struck a chord we are all concerned about in the education issue. And I just wanted to say that I do not think we have any time to waste.

The cystic fibrosis issue has brought this very much to the forefront. There are 200 million people in the U.S. at risk for being carriers. Companies have already lined up to start offering carrier screening tests, and we as a society are in no way prepared to deal with the issues of what this test means, and whether people want it at all. And if they do, and if they get a positive result, what does that mean to them? I am really quite concerned about this need for rapid education of the public.

As has been pointed out by Dr. King, we do not have a long, wonderful track record in screening for recessive diseases. What happened with sickle cell anemia is a travesty that we really must not repeat.

I am concerned that the time is growing very short to get this sort of issue onto the table, and that the people who might know the most about this are not yet involved.

Dr. WEXLER. Could I just add one follow-up remark to that?

When the initial screening for thalassemia came out in Sardinia where there is a great deal of this illness, they instituted carrier screening and some rudimentary education suggesting that carriers not marry carriers. Well, the effect was that those who found they were carriers were stigmatized, so they became less desirable marriage partners. So the people who weren't carriers, married each other, leaving only the carriers to marry carriers, who would produce affected children.

So I think that this just underscores how essential it is that you give the education in the vocabulary and the metaphors of the people for whom it is intended, because that is exactly what you do not want to have happen.

Senator GORE. Well, in this context, let me return to an example I cited in my opening statement.

Recently, the Senate passed the Americans with Disabilities Act, historic legislation protecting the rights of the disabled and defining the term disability to include persons "regarded as having an impairment in addition to those with an impairment that presently limits a major life activity."

Now, some who have studied the Act are of the opinion that those who test positive to a genetic disorder but have shown no

symptom of illness or disability, would nevertheless be covered under the Act's provisions.

This reading of the Act is reinforced by an example in the legislative report which explains that an individual who has had a back x-ray that shows evidence of a back problem, but who does not presently suffer a back disorder, would still be covered.

I wonder if any of you have had a chance to look at that, if any of you agree or disagree with the analysis?

Ms. KING. Was the language, Senator, impairment that limits a major life activity?

Senator GORE. And regarded as having an impairment. Now, that is in addition to those with an impairment that presently limits a major life activity.

Ms. KING. Right. It seems to me that the language is ambiguous; it is capable of being interpreted to cover those persons who have been identified as having—

Senator GORE. That is so unlike the Congress.

Ms. KING [continuing]. A susceptibility to a future problem. Yes, it is so like the Congress, and I can appreciate that.

But I think in this area it might be useful to be clear.

It seems to me that the legislation does cover and probably was intended to pick up those who had been infected with HIV virus. But it is not clear to me that it is intended to cover someone who may be diagnosed for example, as having a propensity for heart disease. One, that is asymptomatic and, two, it is not necessarily limiting in terms of major life activities.

On the other hand, that does not mean an insurance company would give you a health coverage or a disability coverage or other kinds of coverages if they were aware of that information.

I have not had a chance to look at the disabilities act so I am not an expert.

Senate GORE. All right. Well, it has not finally passed yet. Let me just say that, it has passed the Senate, but it will come back after the conference.

I have asked the committee staff on the other committee whether genetic testing was taken into account and I get the impression that, really, it has not been. I think that it serves as an example of how these discoveries and developments will change a wide range of laws and programs, insurance policies, legal obligations, et cetera.

Dr. WEXLER. If I could make a follow-up comment?

I think that this wording is somewhat similar to a section in the Rehabilitation Act. And I know the genetic disease groups were quite hopeful that that would, in fact, protect them in just such circumstances in which they would be identified as having, or having in the future, genetic conditions.

I think that it would be imperative, if not in this language, in some other language, to have that protection, because it is against discrimination, which would be the unfair use of this information.

If someone is currently capable of performing an activity, then the fact that they may have a liability to develop heart disease or cancer, or even schizophrenia or Alzheimer's in the future, I think should not be held against them.

I think that we should consider whether we want to look at functionality as the criteria and not potentiality, particularly in instances in which there may be appropriate treatments.

Senator GORE. Well, let me raise another question. What about malpractice?

We currently have a set of behaviors called defensive medicine, where doctors feel obliged to conduct a variety of tests in order to protect themselves against malpractice.

If the Human Genome Initiative makes it clear that tests could discover information that could be useful to a doctor in choosing the appropriate treatment for his or her patient, at what point does the legal obligation to conduct a genetics screening kick in with the threat of a malpractice suit if the test is not conducted?

Ms. KING. After the first case against the first doctor—that is won against the first doctor.

But I think that this is a serious problem. I think that the theory of malpractice is designed to protect physicians.

The theory is that you are not obligated to undertake these tests until they are standard practice.

The reality is that, what I jokingly referred to, the first lawsuit that is won is the reality, and physicians will, indeed, want to use these tests more in the future.

I actually think that the propensity is likely to increase.

There are some who argue that the current posture of wrongful birth and wrongful life suits distorts the abortion question because it only permits recovery for those parents who have decided that they would have had an abortion if they had been informed.

If we can develop a way for saying that parents should be informed, period, whatever their intention. If it is just to prepare for the birth of a child who is going to suffer some disabilities, that they too should be entitled to recover.

We are talking about an expansion in malpractice, but at least in those circumstances, I think an expansion that is warranted and one that wouldn't heavily weigh towards using abortion.

I think that Dr. Wexler pointed to the problem of the time lags between diagnosis and possible development of therapeutic measures. One of the reasons that is controversial, in addition to all the ones that she talked about, was that, in the reproductive area, that makes abortion for many the only viable option.

And it seems to me that we are going to have to do something with not having abortion as the only available option; that we have to support parents who wish to have children who may have susceptibilities to certain problems, because that is their choice. And they currently have no support and no resort to the legal system.

Dr. WEXLER. I think that the obligation to inform kicks in very early and the obligation to conduct kicks in later.

Senator GORE. The obligation to inform?

Dr. WEXLER. To inform. That if these tests are available, that standard practice should be that the physician inform patients: I can do this test; I can do that test; it will have these consequences; we can do X, Y, Z, if you test this way.

And that information should go—also prior to childbearing, because for those couples who do not choose to have an abortion, they may choose not to have children if they know the information.

To conduct the test, and particularly these kinds of tests, I think may require a lot more careful thinking about informed consent. We typically do not get informed consent for routine medical tests. But for certain kinds of tests we might consider doing that, or at least requiring better information-giving on the part of the physician and have that be integrated as part of the standard practice for which the physician is responsible.

People, with some genetic tests, for the Huntington's test, people will call Columbia, where we were giving the test and say, you know, I do not know if this patient is crazy or Huntington's. Can I just send him over and would you test him?

Now, I think that is not good practice, and the physician is certainly not giving the required information to, in this case, his patient.

So, physicians will use these tests in a kind of willy-nilly fashion without informing their patients of the possible consequences of the information. And once the test is there and the information is there, it is very difficult not to either convey the information or then *ex post facto*, have to deal with the consequences.

Senator GORE. Does the obligation to inform carry with it an obligation to counsel?

Dr. WEXLER. Yes. To me I think you cannot penetrate somebody else's brain with the information unless you also couple it with counseling. I think that is another problem again in medical school, is that that often is not well taught in the medical schools, is how to interview and how to really give your patients information in a way that they assimilate it and not tune it out.

Senator GORE. So really what we are seeing here is an ethical Heisenberg principle. We cannot observe the human genome without changing our relationship to it in very profound ways.

There are also questions about how the Federal Government applies such genetic tests.

It could be argued for example that it is in the public interest to screen airline pilots to ensure that they are not especially prone to heart attacks. But what about a pilot's right to privacy and his right not to know whether he has such an affliction.

Indeed, the kinds of questions that come up multiply rapidly when you get into prenatal screening, genetic screening by employers, genetic screening by insurance companies, confidentiality of the results, malpractice, as I mentioned. How do we balance the need to commercialize new products based on the sequencing data with the need to publish and share that data? It really is going to be a Pandora's Box in so many different ways.

The case for applying an adequate level of resources to the effort to answer these questions, or at least to map the answers so we can see the chromosomes of the answers, if not the genes or the base pairs.

It is imperative that we do that. I am not even going to get into the abortion questions that were referred to earlier because we could spend a lot of time on that.

I think the Congress has obligations to deal with these ethical issues and societal issues, as well; not just in hearings like this one, but in a more sustained way. In that regard, I hope and expect that

this subcommittee will, in the coming year, have a series of more detailed and focused hearings on these questions.

Let me ask just two more brief sets of questions.

First of all, Dr. Olson, what are the major technical obstacles now confronting the project, and what can be done at a management and organizational level to overcome them?

Dr. OLSON. Well, I think that this technical question calls for a technical answer.

The physical mapping has already been identified as the high priority for the next few years; this is the business of identifying landmarks along the chromosomes, the order or the landmarks, the intervals between them, and getting landmarks at a useful density, which probably will require on the order of, let us say, 50,000 landmarks to be met.

All of the existing techniques for doing that which have shown promise to work on this scale, depend on recovering the DNA and recombinant DNA molecules.

And I would say that one of the technical uncertainties about the—not so much the success of this project but the quality of the resultant map, has to do with what fraction of the DNA can be recovered with existent recombinant DNA systems.

I think we do not know the answer to that question, and the quality of the map will be heavily dependent on the frequency at which material is present that cannot be recovered in this way. I see that as the major obstacle to the physical mapping.

I am not sure that it calls for any new managerial policies. I think that that is why they recognized that that is a key problem and proponents of various particular recombinant DNA technologies here are working rather actively on it.

I think the genome office is aware of that that is an important subject.

With respect to sequencing, I think there is an increasing view that at least the initiation of this project is going to involve technologies that are only incremental improvements over ones that we already have, and that is going to put a lot of pressure on a very diversified set of approaches to improving sequencing and trying to drive the cost down.

I think that also is going on rather well, partly due to the efforts of the genome office, but also you should appreciate that a tremendous amount of DNA sequencing, in fact, most DNA sequencing that is now done goes on outside of the auspices of this project. And actually it represents a non-trivial commercial market for biochemical reagent kits, instruments and so forth.

And I think that much of the best work in that area is being done by small companies catering to this market.

And that this does pose a more general issue about the human genome project, is that, I think that one of the infrastructure benefits of fairly aggressive funding of this project is that it will create a sizable market for highly entrepreneurial ventures catering to such esoteric matters as sequencing kits and sequencing instruments.

And in the long run, some of those entrepreneurial ventures are likely to become, sort of biotechnology companies of the future.

Senator GORE. Well, that is very helpful. Thank you.

Let me ask a little more about the international data exchange problem.

What do you think of Dr. Watson's suggestion that the Japanese not be given access to the sequence data unless they do their fair share of the research?

Dr. OLSON. I personally am strongly opposed to having different rules for one set of scientists as opposed to another set of scientists, however we resolve this issue of how long the laboratory that actually originates the data will have some control over it, some opportunity to analyze it before it is published.

I do not believe that there should be more than two categories of access to the data, one associated with the laboratory that originates it and the other associated with the rest of the scientific community, regardless of nationality.

Senator GORE. Well, they have separate rules for us.

Dr. OLSON. Will they have or do they?

Senator GORE. They do.

Dr. OLSON. They do have. In genetics you mean or are you speaking more broadly?

Senator GORE. I am speaking more broadly. Do they not?

Dr. OLSON. I am sure you know more about that subject than I do. I am not aware of—within basic scientific research in the fields that I am acquainted with, I am not aware of them having separate rules with respect to us.

Senator GORE. Well, I will elaborate for the record if it is necessary, but I think that there are plenty of places where they do. But I accept and respect your view that there should not be, in your opinion, two separate sets of rules.

Dr. Collins.

Dr. COLLINS. I think I would probably come down somewhere between the two views.

I think it is—

Senator GORE. Are you thinking of going into politics, Dr. Collins?

Dr. COLLINS. I think it is impossible to imagine recruiting bright, talented, young scientists to work on this project if they do not have some assurances of a first crack at the data. I mean that is just a given.

Senator GORE. Yes.

Dr. COLLINS. And that means that you will not be feeding the output of your sequencing machine into a data line for everybody else to analyze that day. That just will not work. Nobody will want to do that job.

Senator GORE. Yes.

Dr. OLSON. I think we all agree with that.

Dr. COLLINS. So then the question is, how long does it take to have that first crack at it, and do you then immediately release the data.

I am not sure that one ought to decide that right now. The negotiations are still going on to find out how much effort the Japanese are going to put into this.

As soon as we decide precisely what the U.S. is going to do about release of the data, the Japanese motivation for coming up with a little more input will go away.

Perhaps, therefore, it is best to leave things a bit vague for the time being, with the implication that this is not necessarily going to be a freebie.

Senator GORE. Well, I think that is a sensible statement.

I want to reiterate as well that we intend to explore this territory more thoroughly in the coming year. I want to again thank all of our witnesses for the fine presentations that you have given to us here today. We appreciate it, and the hearing will be adjourned.

[Whereupon, the subcommittee was adjourned at 1:35 p.m.]

